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SODIUM NITROPRUSSIDE
INDUCED HYPOTENSION
DURING
HALOTHANE ANAESTHESIA
Clinical and experimental studies on
the influence
on blood loss, lung function and
haemodynamics

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Malmö 1983

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by

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Forsan et haec olim meminisse iuvabit.

(Vergilius)

The present dissertation is based on the following publications,
which will be referred to in the text by their Roman numerals:

I. ANESTHETIC TECHNIQUES AND SURGICAL BLOOD LOSS IN TOTAL
HIP ARTHROPLASTY.

In collaboration with H. Fredin and B. Rosberg.

Acta Anaesth Scand 26, 189-193 (1982)

II. HAEMODYNAMICS AND PULMONARY DEAD SPACE DURING SODIUM
NITROPRUSSIDE INDUCED HYPOTENSION AND HIP ARTHROPLASTY.

In collaboration with B. Rosberg.

Submitted for publication in Br J Anaesth.

III. CENTRAL HAEMODYNAMICS AND REGIONAL BLOOD FLOW DURING
HALOTHANE - NITROUS OXIDE ANAESTHESIA AND CONTROLLED
VENTILATION.

In collaboration with K.F. Aronsen, J. Idvall and
B. Rosberg.

Res Exp Med (In press) 1983.

IV. CENTRAL AND PERIPHERAL CIRCULATION DURING AND AFTER
SODIUM NITROPRUSSIDE INDUCED HYPOTENSION IN THE RAT.

Submitted for publication in Br J Anaesth.

V. CIRCULATORY EFFECTS OF HAEMORRHAGE DURING SODIUM
NITROPRUSSIDE INDUCED HYPOTENSION.

In collaboration with K.F. Aronsen and B. Rosberg.

Submitted for publication in Acta Anaesth Scand.

The following abbreviations will be used in the text:

a-v = arterio-venous

CO = cardiac output

HR = heart rate

LCW = left cardiac work

MAP = mean arterial pressure

NLA = neurolept analgesia

PAMP = pulmonary arterial mean pressure

PCW = pulmonary capillary wedge pressure

PVR = pulmonary vascular resistance

SNP = sodium nitroprusside

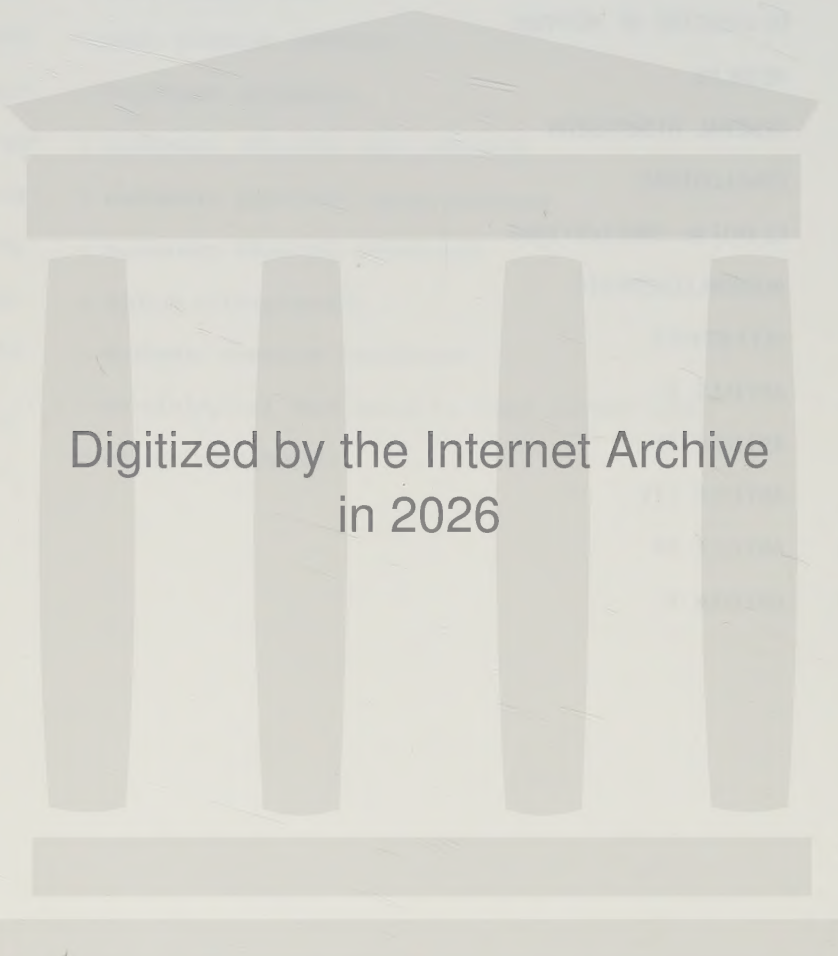
SVR = systemic vascular resistance

V_D/V_T = physiological dead space to tidal volume ratio

$\dot{V}_{O_2}$ = oxygen consumption

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INTRODUCTION

Techniques to diminish the need for bank blood during surgical procedures include hypotensive anaesthesia, haemodilution and varieties of autologous blood transfusions. Of these alternatives, induced hypotension has the advantage of not only reducing the risk of and need for transfusion, but also facilitating the surgeon's work.

Early methods to deliberately reduce systemic blood pressure included arteriotomy (Gardner 1946, Mortimer 1951), with temporary removal of up to 3 000 ml of blood, and total spinal block (Griffiths and Gillies 1948), where arterial blood pressures were often unrecordable for a time.

Adequately controlled hypotension started with the introduction of pentolinium (Davison 1950, Enderby 1950), followed by other α -ganglionic drugs, which gave satisfactory conditions for both the patient and the surgeon.

Today short-acting vasodilators, such as sodium nitroprusside (SNP), are recommended in hypotensive anaesthesia (Lindop 1975). Sodium nitroprusside was first synthesised by Playfair in 1849, and its hypotensive action was demonstrated in animals by Herrmann 1886. Johnson (1929) found that SNP acts by a direct dilation of vascular smooth muscle. Since the introduction of SNP in clinical practice it has gained widespread use (Page 1951, Moraca et al. 1962, Stoelting et al. 1977, Beierholm et al. 1983).

Hypotension induced by SNP is quick in onset, readily controllable, and evanescent upon withdrawal of the drug. It does not impair myocardial contractility (Adams et al. 1973), but reduces afterload making it useful also in the treatment of severe heart failure (Miller et al. 1977, Cohn and Franciosa 1976).

The major risk of hypotensive anaesthesia is attributed to a deficient oxygen delivery to vital organs, as a result of re-

duced blood flow and/or disturbed arterial oxygenation. There are only a few studies concerning whole-body distribution of cardiac output during SNP induced hypotension (Miletich and Ivankovich 1978, Delaney and Miller 1980, Hoffman et al. 1982).

Rebound hypertension may follow withdrawal of SNP, as reported by Miller et al. (1977), Khambatta et al. (1979), and Rudehill et al. (1979). To date there are no published reports dealing with central haemodynamics and regional blood flow following withdrawal of SNP.

Hypovolaemia and uncompensated blood loss are considered a great hazard, especially during SNP induced hypotension (Edwards and Fleming 1975). Studies have been performed on animals with impaired ability to vasoconstrict caused either by surgical sympathectomy (Schlossberg et al. 1933, Brooks 1935) or adrenoreceptor blocking drugs (Jacob et al. 1956, Baez et al. 1958). The results differ regarding the tolerance of these animals to haemorrhage. Circulatory consequences of acute hypovolaemia during SNP induced hypotension have never been elucidated.

Hypotension from different causes has been shown to increase pulmonary dead space (V_D/V_T) (Freeman and Nunn 1963, Eckenhoff et al. 1963, Askrog et al. 1964). It has recently been shown (Khambatta et al. 1982) however, that V_D/V_T does not increase in patients during SNP induced hypotension, provided cardiac output is maintained. That study was performed with patients in the prone position. The pulmonary effects of controlled ventilation in the lateral position imply a redistribution of the ventilation from the dependent to the non dependent lung (Wulff and Aulin 1972). There is no information on the V_D/V_T ratio during hypotension in the lateral position, which has a more pronounced hydrostatic effect on pulmonary circulation (Nunn 1969).

AIMS OF THE STUDY

The aim of the present investigation was to further elucidate the effects of SNP induced hypotension during halothane anaesthesia on surgical blood loss, central and regional haemodynamics and lung function.

The clinical part was designed to study SNP induced hypotension during halothane anaesthesia, applied during total hip arthroplasty, with special regard to:

Anaesthetic technique and surgical blood loss (I)

Central haemodynamics during major surgery (II)

Physiological dead space (II)

The experimental part was designed for the following studies:

A well defined anaesthesia model for the rat (III)

Central haemodynamics and fractional distribution of cardiac output, during and after SNP infusion (IV)

Circulatory effects of haemorrhage during SNP infusion (V).

MATERIAL

Clinical part:

Patients with osteoarthritis of the hip, scheduled for primary total hip arthroplasty were selected for the study. Paper I deals with 157 patients (Table I, page I:2), subdivided into four groups. The first two groups contain 61 patients. They showed no signs of cardiovascular, pulmonary, renal, hepatic, or thyroid diseases and were randomly allocated into either intentional hypotensive anaesthesia with halothane and SNP, or normotensive halothane anaesthesia. The latter two groups comprise 96 patients with concomitant systemic diseases. They were operated upon either during epidural

block (group III) or neurolept analgesia (NLA) (group IV), according to the decision of the anaesthesiologist.

Paper II deals with 22 otherwise healthy patients, scheduled for total hip arthroplasty in the supine or in the lateral position. They were randomly allocated into either normotensive halothane anaesthesia or hypotensive anaesthesia induced by SNP.

The investigation was approved by the Committee of Ethics, University of Lund.

Experimental part:

Fortytwo male Wistar SPF rats, weighing 165-345 g were studied (papers III, IV, V).

The experimental investigation was approved by the Regional Committee of Ethics in Animal Experiments.

METHODS

Anaesthesia

In paper I halothane/ N_2O anaesthesia with controlled ventilation was used for 61 patients. Continuous epidural block with a sensory distribution to T_6 was applied in 79 patients. Supplementary slight sedation was provided by either diazepam, hexobarbital infusion, or a combination of droperidol and fentanyl. A neurolept analgesic technique (NLA II, Nilsson 1963) was used in 17 patients.

Halothane/ N_2O anaesthesia was applied also in the 22 patients in paper II.

The rats (papers III, IV, V) were anaesthetised with a mixture of halothane 1 %, N_2O and O_2 (3:2) through a tracheotomy, and placed supine.

The halothane concentration was repeatedly checked spectrophoto-

metrically (EMMA, Engström Medicals, Sweden) and found to remain constant. The body temperature of the animals was kept at approximately 37°C during anaesthesia, by the aid of a conventional lamp.

Ventilation

All patients, except those with epidural block, were artificially ventilated (ECS 2 000, Engström Medicals, Sweden) at a rate of 20 bpm. Tidal volumes were calculated according to Engström and Herzog (1959). The ventilator settings were not changed during anaesthesia.

The rats were ventilated by means of a small animals' ventilator (Braun AG, Melsungen, Germany) at a rate of 80 bpm. Tidal volumes were adjusted to an arterial PCO_2 of 4.0 - 4.5 kPa. The settings were not changed during anaesthesia.

Catheterisation

All patients, except those with epidural block, had a radial arterial catheter inserted percutaneously (Venflon 1.2 mm, Viggo AB, Sweden). In addition, the patients in paper II had a triple lumen catheter (93-1177-7-F, Edwards Lab., St. Ana, Calif., USA) inserted into the pulmonary artery.

The rats were catheterised during anaesthesia. A polyethylene catheter (PE 10) (Sasaki and Wagner 1971) was inserted into the left ventricle of the heart via the right carotid artery. The correct position of this catheter was verified at necropsy. Femoral arteries and veins were exposed and PE 90 catheters, with their tips tapered according to Idvall et al. (1979), were inserted into the caval vein and abdominal aorta. The catheters were flushed with heparinised saline.

In ten rats (paper III) the first sets of measurements were performed in the conscious state. Catheters were inserted under ether anaesthesia, tunnelled subcutaneously, exiting via a neck incision.

After protecting the exposed portion of the catheter with a hard plastic tube, it was flushed with heparinised saline and clamped. The rats were left to recover for 12-24 hours in a special cage (Bergman and Husberg 1980) which allowed free movements and access to water and food. Following haemodynamic measurements while conscious, the rats were anaesthetised with halothane/N₂O.

Pressure recordings

In the clinical study, arterial blood pressure was continuously recorded using a transducer (Ailtech, Cutler & Hammer Co., Calif., USA) connected to the arterial catheter. The same type of transducer was used to register pulmonary arterial pressure and pulmonary capillary wedge pressure (paper II).

In the epidural group (paper I) arterial blood pressure was measured by a conventional blood pressure cuff.

In paper I, mean arterial blood pressure (MAP) was calculated from the formula:

$$\text{MAP} = \text{diastolic pressure} + \frac{\text{systolic pressure} - \text{diastolic pressure}}{3}$$

In the rats, MAP was recorded using a transducer (EMT 34, Siemens Elema, Sweden) connected to the aortic catheter.

Heart rate(HR) was calculated from the ECG recordings in the clinical study, and from the pressure recordings in the experimental study.

Cardiac output (CO) was determined using a dye dilution technique (Wassén 1956) (paper II).

In the experimental study CO was determined by the reference sample method (Archie et al. 1973, Malik et al. 1976, McDevitt et al. 1976, Idvall et al. 1979). Simultaneous with the injection of microspheres, blood was withdrawn from the aortic catheter, at a rate of 0.6 ml/min for 30 seconds, using a withdrawal pump (model

351, Sage Instruments, Cambridge, Mass., USA). Cardiac output was calculated using the formula:

$$CO = \frac{\text{counts injected} \times \text{reference sample withdrawal rate}}{\text{reference sample counts}}$$

Determination of organ blood flow

The fractional distribution of cardiac output was assessed according to the microsphere technique (Rudolph and Heymann 1967), using a modification (Svedman 1977, Idvall et al. 1979) that has proved valid for investigations in the rat.

Microspheres type NEN-TRAC (NEN Co., Mass., USA) are made of inert plastic material and labelled with either ^{46}Sc or ^{103}Ru . Their diameter is 15 ± 1 (SD) μm and their specific gravity approximately 1.3. The spheres were suspended in dextran with one drop of Tween 20 added to prevent aggregation. The microspheres were mechanically agitated immediately before the injection to ensure even distribution. Depending on the actual radioactivity $1-2 \times 10^5$ spheres were injected into the left ventricle for each determination.

Regional blood flow. Total amount of injected radioactivity was determined by measuring the whole rat in a Marinelli Chamber with a 4×3 inch thallim activated sodium iodide crystal placed 20 cm from the center of the specimen. The detector was connected to a gamma spectrometer (Canberra model 818) with the window settings at 450-550 keV (^{103}Ru) and 700-1 000 keV (^{46}Sc). Animal standards were used to correct for the overlapping of the isotopes. The organs were removed, weighed and put into small plastic tubes. Large organs were divided. The inner layer of the left ventricle of the heart and the valvular cusps were excised to obtain a correct value of myocardial blood flow (Idvall et al. 1979).

Concentrated sulphuric acid was added to homogenise the tissue and to produce identical volumes, in order to minimise geometrical error. The activity of the specimens was determined in an automatic

well counter (2x2 inch well crystal, Nuclear Chicago) connected to a gamma spectrometer (Ultrascaler 2, Nuclear Chicago). Standard solutions containing only one isotope each were used to correct for overlapping of the isotopes. Carcass activity was determined in the Marinelli Chamber after organ removal.

The fractional distribution of CO was calculated by dividing the radioactivity recorded in each organ by the total activity of the isotope injected. Organ blood flow was obtained by multiplying CO with the fractional distribution of CO to each organ.

The sum of values found for stomach, spleen and intestine was taken as the value for the preportal area, while total liver blood flow is defined as the sum of the preportal and hepatic arterial flows.

Arterial and mixed venous blood gas tensions and pH

In patients, blood was collected in heparinised glass syringes, and analysed at 37°C (IL M113, Boston, Mass., USA). The values were corrected to the actual body temperature (paper II).

In the rats, 0.5 ml of arterial blood samples were analysed (ABL 1, Radiometer, Denmark). No correction for temperature was performed since the animals were kept at a body temperature of approximately 37°C (papers III, IV, V). Blood samples used for analysis were replaced by a 3-fold volume of saline.

Haemoglobin concentration was analysed spectrophotometrically (Vitatron, Kistner AB, Sweden) in the clinical study.

Haematocrit was determined in duplicate using 20 μ l of blood (papers III, IV, V). The heparinised microtubes were centrifuged at 1 000 g for 10 minutes. Values obtained were not corrected for trapped plasma.

Derived haemodynamic variables

Systemic vascular resistance (SVR) was calculated as $\frac{MAP}{CO}$

Pulmonary vascular resistance (PVR) was calculated as $\frac{\text{PAMP-PCW}}{\text{CO}}$

Oxygen content (C_{O_2} , STPD) was calculated from the formula:

$\text{C}_{\text{O}_2} = \text{Hb} \times \text{SO}_2 \times 1.34 + \text{PO}_2 \times 0.23$ (Nunn and Freeman, 1964), where SO_2 denotes the saturation of the haemoglobin.

Available oxygen (STPD) was estimated as $\text{CO} \times \text{Ca}_{\text{O}_2}$.

Oxygen consumption ($\dot{\text{V}}_{\text{O}_2}$, STPD) was calculated as a product of CO and arterial-mixed venous content difference.

Carbon dioxide production (STPD) was calculated as a product of expired minute volume and mixed expired CO_2 concentration.

Left cardiac work (LCW) is given as $\text{CO} \times \text{MAP}$ (paper III, IV, V).

Pulmonary dead space calculations (paper II)

Expiratory gas was collected from the expiratory outlet of the ventilator into a polylamine bag (sized 100 l, Svanbergs Tekniska AB, Sweden). During collection the excess scavenging outlet was clamped. The gas volume was measured by a Wright respirometer (Wright 1955).

Tidal volume (V_T , STPD) was calculated by dividing the collected volume by the number of respirations.

Mixed expired CO_2 concentration was analysed from the content of the bag with an infrared CO_2 analyser (Capnograph, Godard, Netherlands).

Physiological dead space (including apparatus dead space) to tidal volume ratio, $\text{V}_\text{D}/\text{V}_\text{T}$ was calculated from a modified Bohr equation (Enghoff 1938)

$$V_D/V_T = \frac{P_a\text{CO}_2 - P_E\text{CO}_2}{P_a\text{CO}_2}, \text{ where } P_a\text{CO}_2 \text{ denotes arterial oxygen}$$

tension and $P_E\text{CO}_2$ mixed expired CO_2 tension.

Blood loss (paper I). Intraoperative blood loss was estimated from the volume of blood in suction apparatus, weighed sponges and drapes. Postoperative blood loss was measured from bleeding collected in suction drains.

Bleeding procedure (paper V). Blood, 10 ml/kg body weight, was withdrawn via the aortic catheter during a period of 2 minutes.

Statistical methods Statistical and mathematical calculations were made on a desk calculator (Hewlett Packard model 8510 A) using HP Stat Pac programs. Comparisons were carried out using the Students' T-test (paper I), the Wilcoxon test for paired observations and the Mann-Whitney test for unpaired observations (paper II,III,IV, V), as appropriate. Degrees of significance are given as follows:
 * $p \leq 0.05$, ** $p \leq 0.01$.

DISCUSSION OF METHODS

Clinical part:

Physiological dead space calculations

In the present investigation the following factors may have influenced the results:

1. Transient pulmonary dysfunction

Hip arthroplasty has been shown to induce transient pulmonary dysfunction in connection with the application of bone cement. These changes, however, are of short duration and pulmonary function is normalised within 10 minutes (Modig and Malmberg 1975, Wulff et al. 1975, Mebius and Hedenstierna 1982). In the present study measure-

ments were performed later than 20 minutes after completed fixation of the femoral prosthesis.

2. Variation in dead space caused by compressed gas

The internal volume of the ventilator, tubings, connectors and humidifier was 1340 ml, corresponding to a compliance of 32 ml/kPa. No correction was made for this dead space. Airway pressure was recorded from the ventilator, but detailed measurements were not performed. Mebius and Hedenstierna (1982) reported raised end inspiratory pressures, averaging 0.27 kPa, during the course of total hip arthroplasty. Such a raise would increase our results of dead space measurements by an average of 9 ml.

3. Carbon dioxide determination

When CO_2 is analysed with the infrared absorption technique, N_2O and O_2 will influence the result by "collision broadening" (Coggeshall and Saier 1947, Fletcher 1980). In order to minimise this error the CO_2 analyser (Capnograph, Godard, Netherlands), was calibrated against known concentrations of CO_2 in 1:1 mixtures of nitrous oxide and oxygen.

4. Tidal volume determination

Wright respirometers have been shown to be inaccurate by up to 20 per cent (Nunn and Ezi-Ashi 1962, Eckenhoff et al. 1963). The respirometer used in this study was repeatedly checked, using different gas flows and volumes, against a volumeter (Juncalor, Grave AB, Sweden) and the difference never exceeded 4 per cent. To avoid pulsatile flow during volume measurements, the bag was always smoothly deflated by the same person.

Cardiac output determination

The potential errors of the dye dilution technique have been thoroughly penetrated by Hamilton (1932). A correlation between the dye dilution technique, as it is carried out in our institution, and the thermodilution technique (Forrester et al. 1972)

showed excellent agreement (Rosberg 1978).

The microsphere technique

The microsphere technique for studies of regional blood flow (Rudolph and Heymann 1967) has been modified for studies in rats (Malik et al. 1976, McDevitt et al. 1976, Svedman 1977, Idvall et al. 1979). The method is well established in our laboratory and offers a possibility to perform sequential determinations in the same experimental animal.

The technique requires that the following basic assumptions are fulfilled:

1. That the microspheres are uniformly mixed with the blood and have essentially the same rheology as red blood cells.

The specific gravity of the microspheres is slightly higher than that of whole blood. The 15 μ m spheres are large enough to be trapped in the capillaries, but so small that they pass any open arterio-venous (a-v) shunt. Obtained values thus represent nutritional blood flow (Wagner et al. 1969).

When the microspheres are injected into the left ventricle, the spheres in the abdominal aorta are well mixed with the blood, as indicated by the good correlation between the radioactivity found in the right and the left kidney.

Idvall et al. (1979) demonstrated that the ventricular injection of microspheres in the rat give an adequate assessment of coronary blood flow only when the inner layer of the ventricle is excised prior to the measurements. This was applied in the present study.

It might be suspected that the ligation of the right carotid artery will reduce blood flow to the brain. Studies of Malik et al. (1976, 1978) demonstrated that if only one carotid artery is ligated, total cerebral blood flow will remain unaffected. If however, both carotids are ligated cerebral blood flow will be reduced, but still remain within physiological limits due to collateral blood flow.

In this study, only the right carotid was ligated.

2. That the injection of microspheres does not affect the blood flow.

It has been shown that repeated injections of 400 000 $15\text{ }\mu\text{m}$ spheres do not alter the distribution of cardiac output in rats (Svedman 1977, Idvall et al. 1979). This was indicated also in this study, most evident in paper III, where repeated injections of microspheres gave similar distribution of CO during stable halothane anaesthesia. When larger spheres, e.g. $50\text{ }\mu\text{m}$, are used, repeated injections could induce significant haemodynamic changes (Warren and Ledingham 1974). The injection of spheres did not cause arrhythmias or changes in systemic arterial pressure.

3. That the microspheres are trapped in the capillaries and do not recirculate.

The trapping of $15\text{ }\mu\text{m}$ spheres in the capillaries is almost complete (Archie et al. 1973). Microspheres passing through pre-portal a-v shunts are trapped in the liver (Ohlsson 1971) and those passing through systemic a-v shunts are trapped in the pulmonary capillary bed (Kaihara et al. 1968). No recirculation of microspheres should therefore be possible.

The radioactivity registered in the liver represents the sum of hepatic arterial flow plus a-v shunting in the gastrointestinal tract. However, according to Ohlsson (1971) there is no significant difference in liver uptake when spheres of 15 ± 5 and of $50\pm 10\text{ }\mu\text{m}$ are simultaneously injected in anaesthetised dogs, while signs of shunting are seen in the stomach.

The radioactivity found in the lungs represent bronchial arterial flow plus peripheral a-v shunting. Considerable systemic shunting of $15\text{ }\mu\text{m}$ spheres have been demonstrated in anaesthetised dogs (Kaihara et al. 1968, Ohlsson 1971, Rosberg and Wulff 1979, Gustafson et al. 1981). In the present study approximately 2 per cent of the total amount of microspheres administered are found in the lungs,

indicating a very low degree of shunting.

4. That there is a sufficient amount of microspheres in each sample.

There must be at least 400 microspheres in each sample, whether this consists of an organ, a tissue specimen, or a "reference organ", to avoid random variations (Buckberg et al. 1971). In this study there was never less than 1 per cent of the total amount of radioactivity in any sample, corresponding to 1 000 spheres.

5. That the amount of radioactivity injected could be accurately determined.

In small animals, like rats, the injected radioactivity is conveniently determined by measuring the whole animal in a scintillation detector.

Determination of cardiac output

When the reference sample method is applied in rats, the microspheres are injected into the left ventricle of the heart. It has been shown by Malik et al. (1976), McDevitt and Nies (1976) and Idvall et al. (1979) that the values obtained using ventricular injections, are in good agreement with those of other methods, such as indicator dilutions (Sapirstein et al. 1960), flowmeters (Pfeffer and Frolich 1972), and direct Fick method (Popovich and Kent 1964).

Bleeding procedure

In experimental studies of haemorrhage, two different methods could be used: either blood is withdrawn until blood pressure falls to a predetermined level, or a fixed volume of blood is shed. The constant pressure model would be disadvantageous for the present investigation, as MAP is affected by SNP. Therefore the rats were bled 10 ml/kg, according to a model previously used in our laboratory (Idvall 1981). The total blood volume of normovolaemic Wistar rats is 70 ml/kg (Idvall 1981). The

haemorrhage thus corresponds to approximately 15 per cent of the blood volume.

RESULTS

Anaesthetic technique and surgical blood loss (I)

Intraoperative blood loss was significantly reduced in patients operated under SNP induced hypotension as compared to those operated under conventional halothane anaesthesia, NLA, or epidural block (Table II, page I:3). In patients with epidural block intraoperative blood loss was reduced as compared to NLA, while no difference was found between epidural block and normotensive halothane anaesthesia.

Postoperative blood loss was significantly higher in the NLA than in the epidural group, while no difference was found between the other groups.

Total blood loss was significantly reduced in the hypotensive group as compared to all the other groups, and in the epidural group as compared to the two normotensive groups.

Regression analysis between MAP half-way through surgery and intraoperative blood loss demonstrated a poor correlation (Figure 2, page:I:2).

Central haemodynamics during major surgery (II)

Mean arterial pressure decreased by 30 per cent to 57 mm Hg (mean) when SNP, mean dose 0.12 mg/kg, was infused during an average operation time of 112 minutes. On withdrawal of SNP, MAP rose above the baseline value. Cardiac output and HR remained unchanged throughout the study, while SVR decreased during hypotension.

Sodium nitroprusside induced hypotension reduced PAMP, while PCW and PVR were unchanged.

Arterial PO_2 decreased during hypotension, but mixed venous PO_2 was unchanged. Standard bicarbonate and pH decreased progressively. Oxygen consumption and carbon dioxide production declined and remained reduced 20 minutes after termination of the SNP infusion.

In the normotensive group CO remained unchanged, while MAP, HR and SVR increased. Pulmonary circulation was unaffected. No change was found in oxygen consumption or carbon dioxide production.

Physiological dead space (II)

When hypotension was induced in patients operated in the lateral position, physiological dead space (V_D / V_T) increased significantly. No such change was found in the normotensive group operated upon in the lateral position.

In the supine groups, hypotensive and normotensive, physiological dead space was unaffected.

Halothane/ N_2O anaesthesia and controlled ventilation in the rat (III)

Central haemodynamic data after one hour of anaesthesia, as compared to the conscious state, are shown in Figure 1. Mean arterial pressure decreased, but no other significant change was found. Arterial blood gases were unaffected.

Increased fractions of CO were delivered to brain and liver (hepatic artery) during anaesthesia. Cardiac output fractions to spleen, stomach and carcass decreased (Figure 2).

Hepatic arterial flow increased, while the absolute perfusion of spleen and stomach decreased. Absolute blood flows to brain, heart, lungs, kidneys, intestine and adrenal glands were unchanged (Figure 3).

When anaesthesia was prolonged from 60 to 90 minutes no further changes in central haemodynamics, fractional distribution of CO, or arterial blood gases occurred.

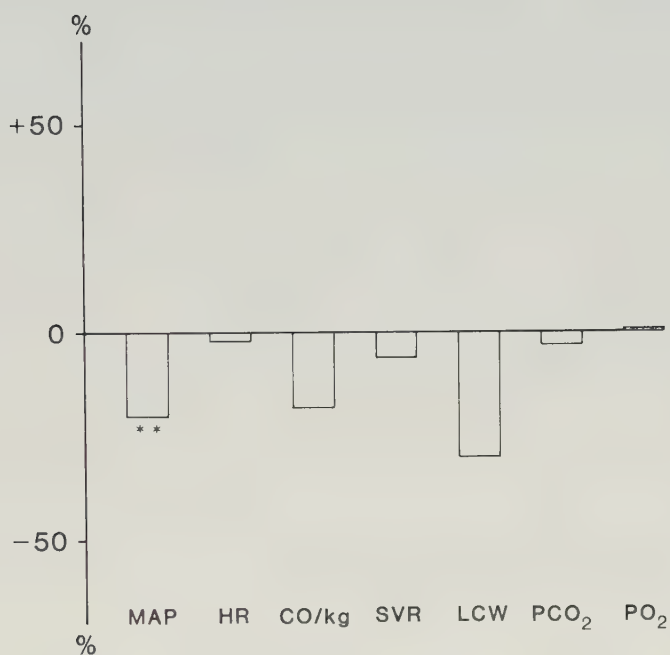


Figure 1. Changes in central haemodynamics and arterial blood gases during halothane/N₂O anaesthesia and controlled ventilation, given as percentage changes from control values in the conscious rat.

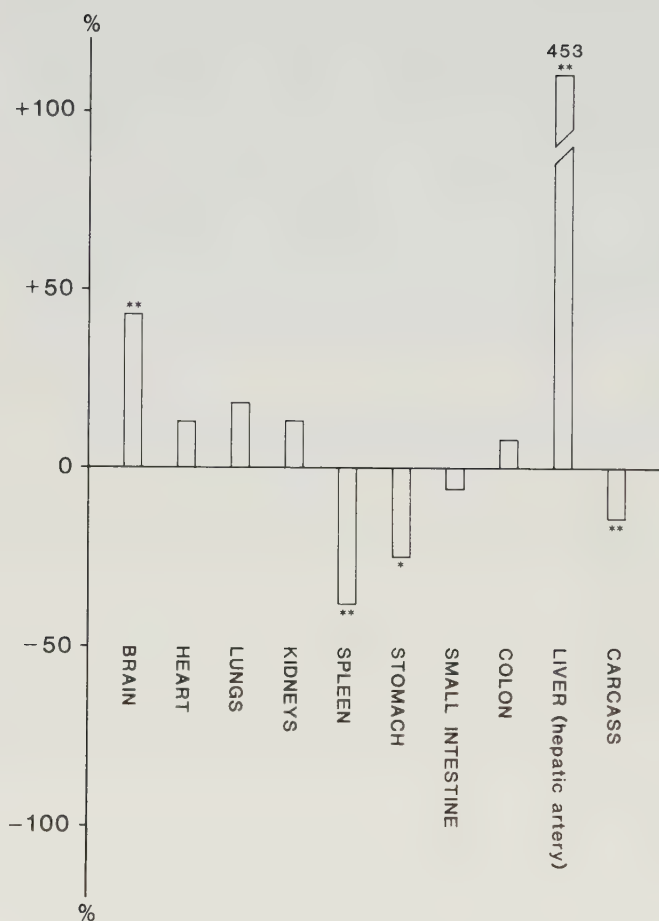


Figure 2. Changes in fractional distribution of CO during halothane/N₂O anaesthesia and controlled ventilation, given as per cent of the control values in the conscious rat.

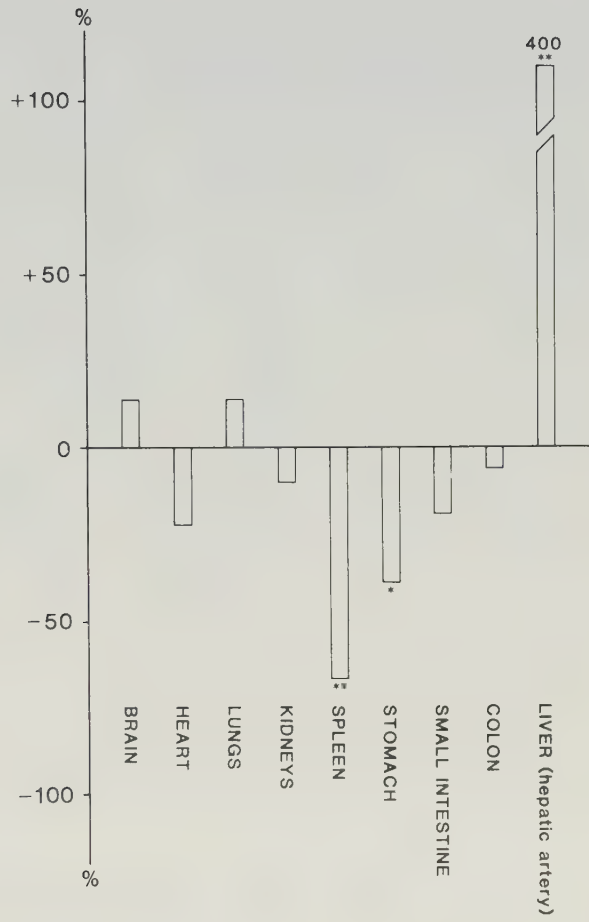


Figure 3. Changes in individual organ blood flow during halothane/N₂O anaesthesia and controlled ventilation, given as per cent of control values in the conscious rat.

Central haemodynamics and fractional distribution of cardiac output during and after SNP infusion (IV).

Changes in central haemodynamics and arterial blood gases, during and after SNP infusion, given as per cent of the control values during normotensive anaesthesia are shown in Figure 4.

The reduction of MAP by 50 per cent to 52 mm Hg was achieved within 1-2 minutes following the start of the SNP infusion. Approximately $40 \mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$ was infused during the hypotensive period (15 minutes). Cardiac output remained unchanged but HR, SVR and LCW decreased significantly.

When the SNP infusion was stopped MAP rapidly returned to, but not above, the initial level. Fifteen minutes later CO and LCW were increased, while HR and SVR remained decreased.

Figure 5 gives the changes in fractional distribution of CO. Fractions delivered to spleen, small intestine and preportal area increased during hypotension, while fractions for the hepatic artery and carcass decreased. The corresponding changes in regional blood flow are shown in Figure 6. Perfusion of spleen and small intestine increased. Hepatic arterial flow was decreased, while preportal and total liver flow increased.

Fifteen minutes after termination of the SNP infusion cerebral, myocardial and renal perfusion were increased and the changes in the splanchnic area persisted.

Circulatory effects of moderate haemorrhage during SNP infusion (V)

Following haemorrhage in the SNP hypotensive rats, CO increased significantly. Mean arterial pressure, HR and LCW were not significantly changed. Absolute values for coronary, renal and hepatic blood flow were maintained or even increased, while blood flow to the carcass was unchanged (Table I-III, page V:8-10).

Following haemorrhage in the control group, MAP, HR and LCW decreased. Cardiac output was not significantly reduced. Blood

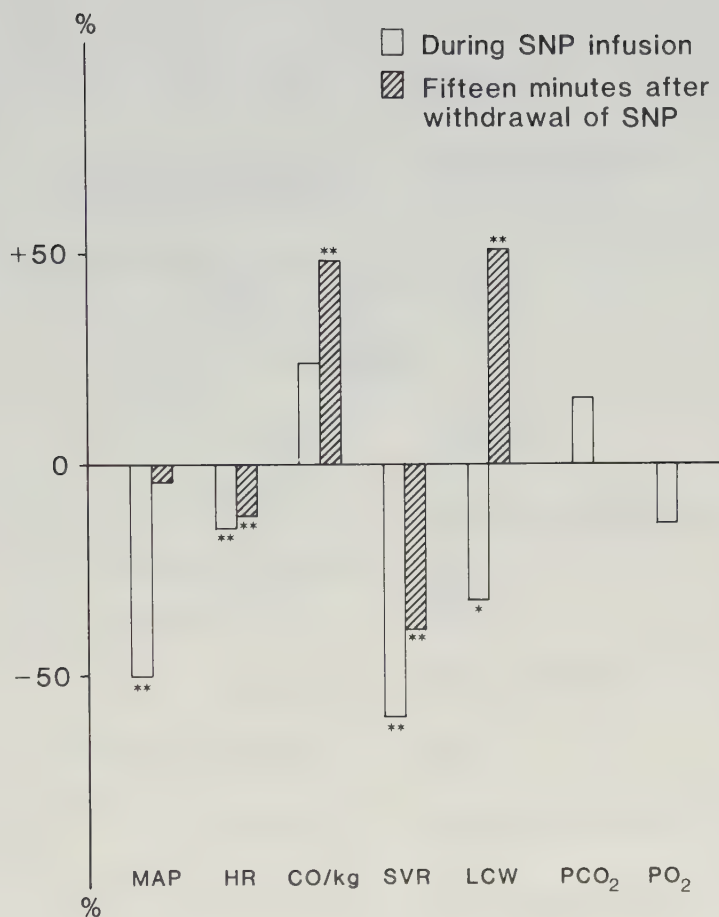


Figure 4. Central haemodynamics and arterial blood gases during and after SNP infusion in the halothane anaesthetised rat. Values are given as percentage changes from the control values during normotensive halothane anaesthesia.

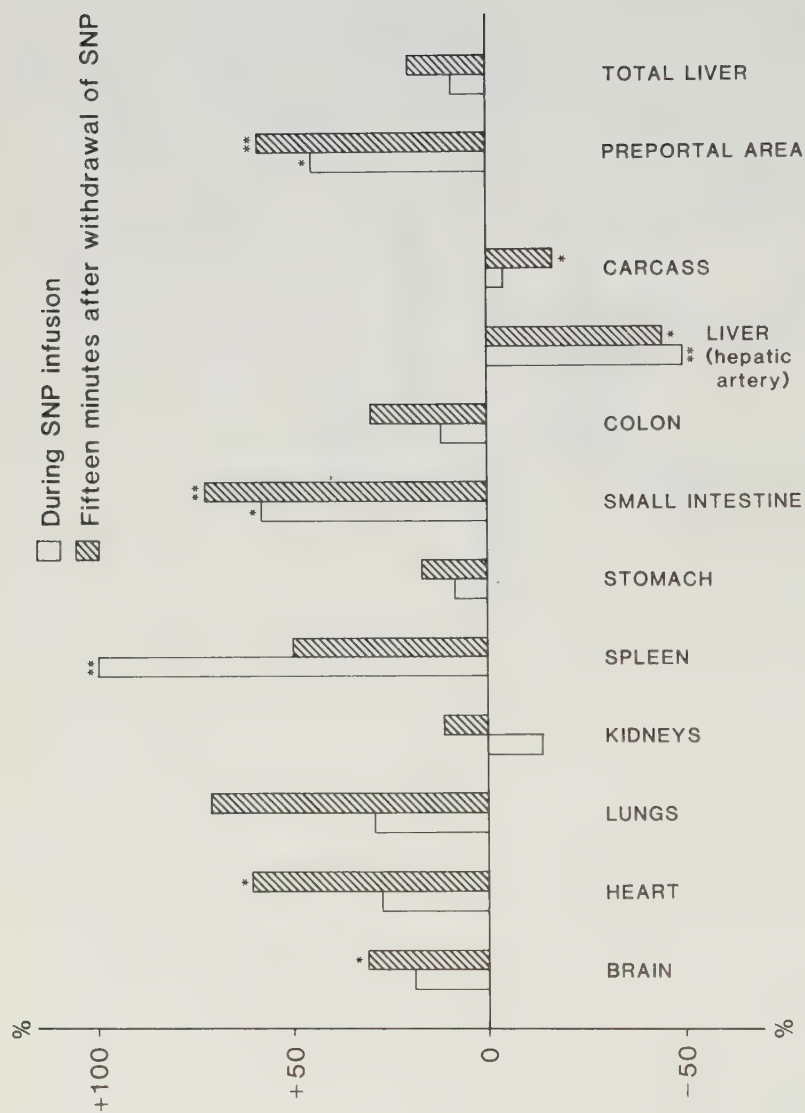


Figure 5. Fractional distribution of CO during and after SNP infusion in the halothane anaesthetised rat. Values are given as percentage changes from the control values during halothane anaesthesia.

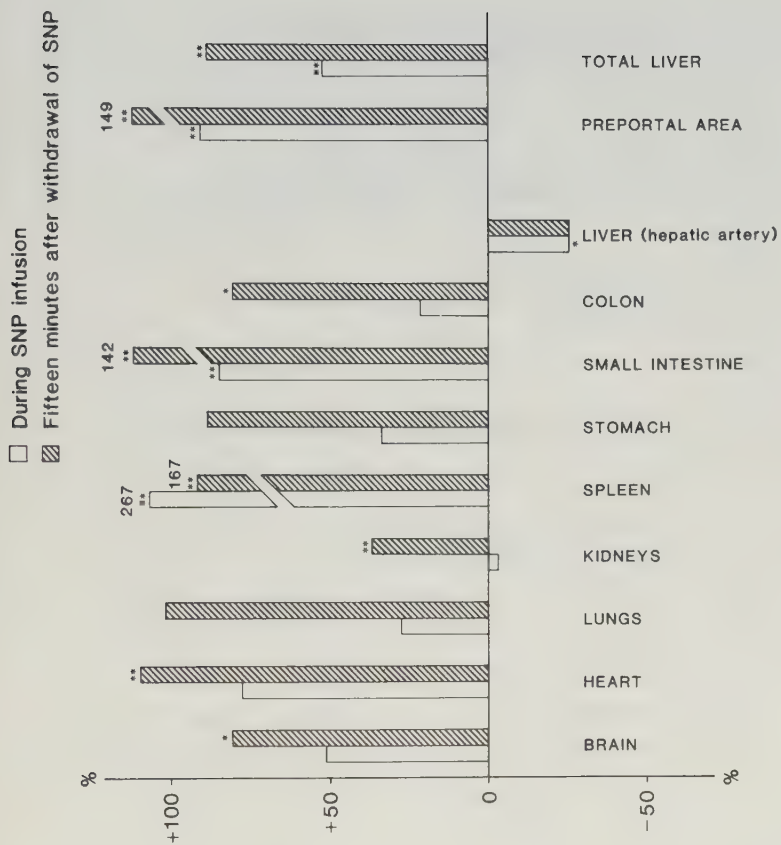


Figure 6. Individual organ blood flow during and after SNP infusion in the halothane anaesthetised rat. Values are given as percentage changes from the values during halothane anaesthesia.

flow was redistributed to favour cerebral, coronary, renal and hepatic circulation, mainly at the expense of a reduction of blood flow to carcass (Table I-III page V:8-10).

Figures 7 - 9 show the circulatory effects of haemorrhage during SNP infusion as compared to control values obtained in the normovolaemic rat during normotensive halothane anaesthesia.

Cardiac output was significantly increased, while MAP and HR were reduced. Fractions of CO delivered to heart, stomach, small bowel and preportal area were greater than control, while lung, kidney and hepatic arterial fractions were less.

Corresponding regional blood flows for heart, spleen, stomach, small intestine, preportal area and total liver were augmented, while lung perfusion was diminished.

GENERAL DISCUSSION

Effects on blood loss in man

Total hip replacement (THR) performed under general anaesthesia and induced hypotension was combined with a significantly lower blood loss than THR performed under normotensive general anaesthesia. The intraoperative blood loss during hypotensive anaesthesia was of the same magnitude as reported by Davis et al. (1974), Lawson et al. (1976) and Barbier-Böhm et al. (1980). It was pointed out by Davis et al. (1974) that hypotensive anaesthesia might be accompanied by an increased postoperative blood loss. In the present study, postoperative blood loss was not greater after hypotensive than after normotensive or epidural anaesthesia. Hypotension induced by SNP can easily be reverted before wound closure, permitting the surgeon to perform haemostasis during normotensive conditions.

Blood loss during THR performed under epidural (Jacobson and

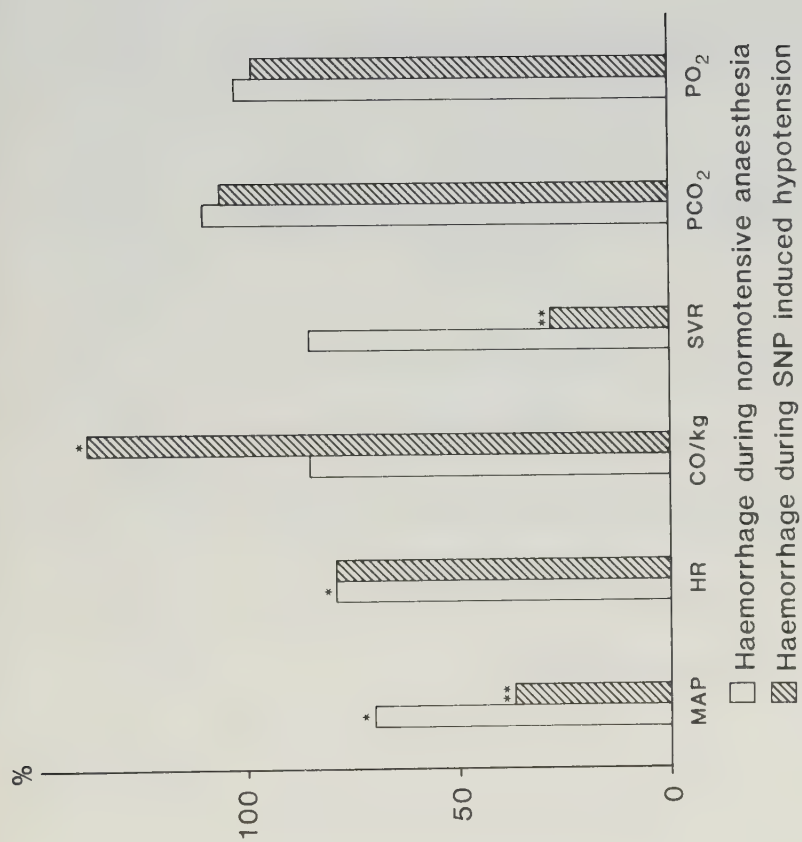


Figure 7. Central haemodynamics and arterial blood gases after moderate haemorrhage in the rat during normotensive halothane anaesthesia and during SNP induced hypotension. Values are given as per cent of values obtained in the normovolaemic rat during normotensive halothane anaesthesia.

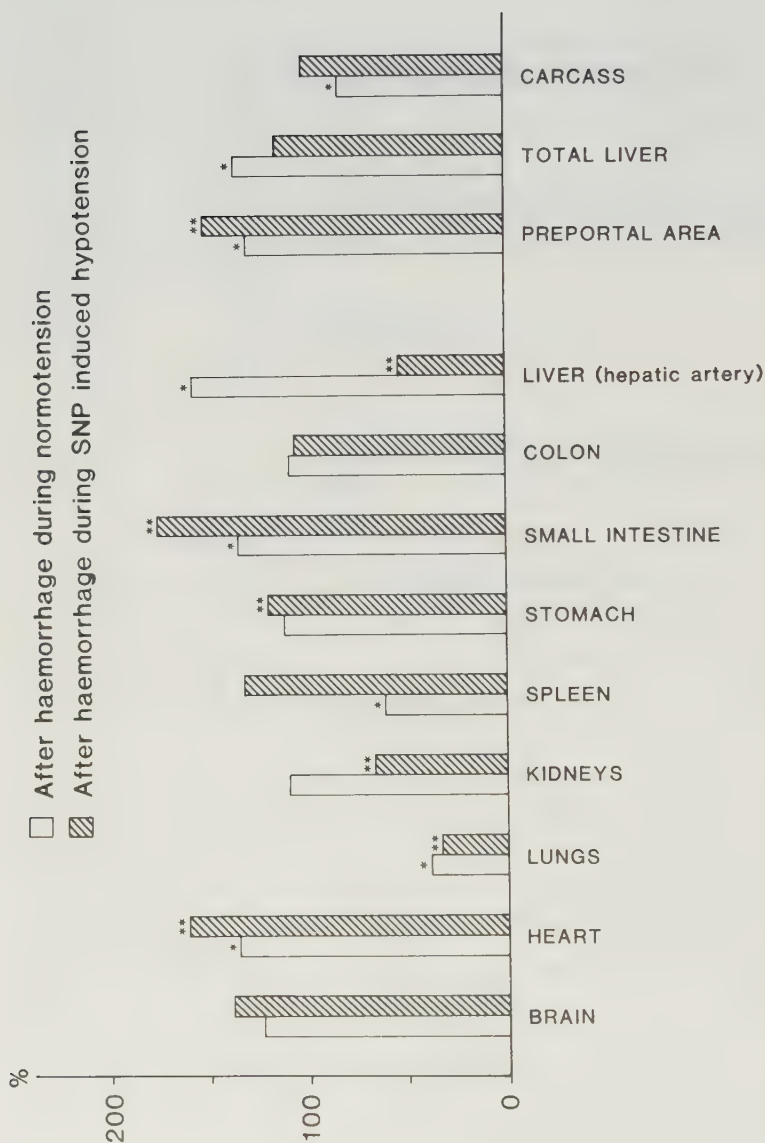


Figure 8. Fractional distribution of CO after moderate haemorrhage in the rat during normotensive halothane anaesthesia and during SNP induced hypotension. Values are given as per cent of values obtained in the normovolaemic rat during normotensive anaesthesia.

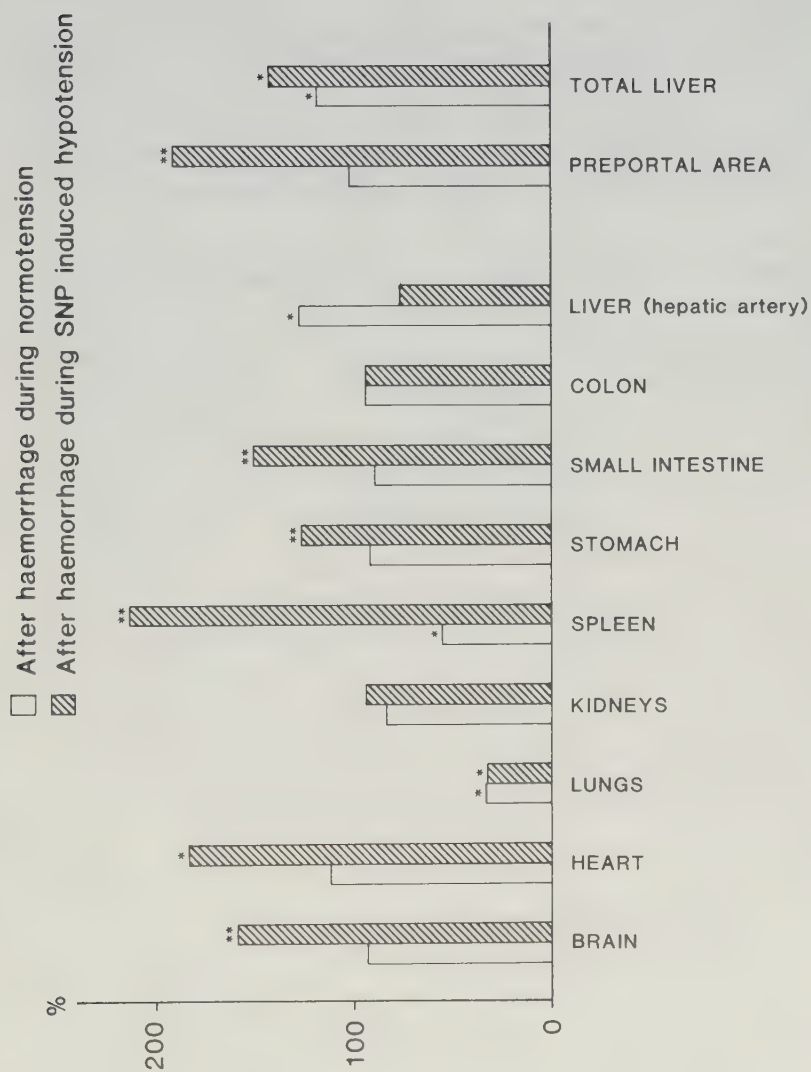


Figure 9. Individual organ blood flow after moderate haemorrhage in the rat during normotensive halothane anaesthesia and during SNP induced hypotension. Values are given as per cent of values obtained in the normovolaemic rat during normotensive halothane anaesthesia.

Wigren 1972) or spinal anaesthesia (Sculco and Ranawat 1975, Thorburn et al. 1980) is less than when normotensive general anaesthesia is applied. These findings are confirmed by the results of the present investigation. However, it must be recognised that in this study the investigated groups of patients differ. Healthy patients, irrespective of age, were randomly allocated to hypotensive or normotensive halothane anaesthesia, while patients showing signs of systemic disease were operated upon under epidural block or NLA.

Regression analysis revealed a poor correlation between intraoperative MAP and blood loss. Donald (1982) suggested that there may exist a MAP below which no further reduction in blood loss can be achieved. When the patients in the present study, regardless of anaesthetic technique used, were rearranged according to their intraoperative MAP (groups A-D, Figure 10), it was found that the peroperative bleeding was significantly lower in group B than in group C ($p \leq 0.05$). No significant difference was found between groups A and B or between C and D.

Other possible advantages of hypotensive anaesthesia include improved operating conditions during e.g. delicate aneurysm surgery (Lagerkranser et al. 1980, Beierholm et al. 1983), or middle ear surgery (Wildsmith et al. 1975). In THR reduced bleeding may improve the fixation of the prosthesis by reducing the interposition of blood between bone and bone cement (Fredin, personal communication, 1983).

Effects on metabolism and central circulation in man

Hypotensive anaesthesia is associated with certain risks such as deficient oxygen supply to vital organs (Fahmy 1978), rebound hypertension (Miller et al. 1977, Khambatta et al. 1979, Rudehill et al. 1979) or overdosage of SNP (Vesey et al. 1975, Cole 1978).

Total oxygen consumption ($\dot{V}_{O_2}$), arterial pH, and standard bicarbonat decreased during hypotension. None of these changes were

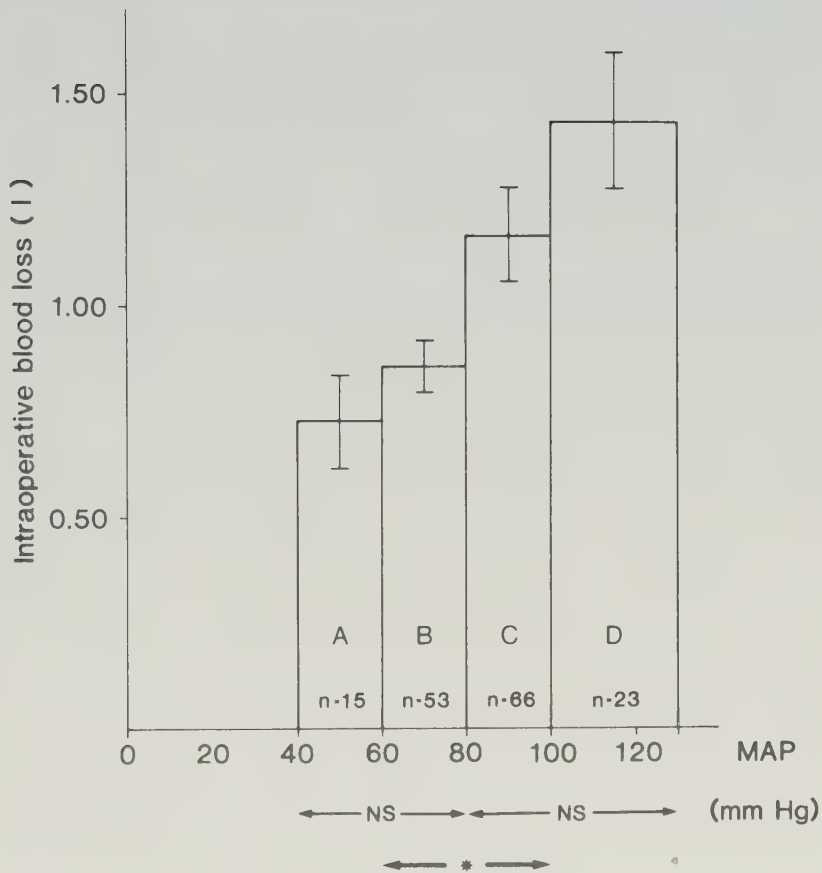


Figure 10. Intraoperative blood loss and mean arterial pressure.
Group B versus group C $p < 0.05$.

found in the normotensive control group. Reductions of body temperature were similar in the SNP group and in the control group. Stone et al. (1976) reported that although CO increased, $\dot{V}_{O_2}$ was unchanged in their study of young patients during SNP induced hypotension. They found no sign of metabolic acidosis. The reason for the metabolic acidosis found in the present clinical study is not clear. A reduced $\dot{V}_{O_2}$ in the presence of an unchanged CO may indicate that SNP induces a-v shunting in the systemic circulation. Indications of increased systemic shunting during SNP induced hypotension were found in experimental animals by Peter et al. (1983), but not in this study. Alternatively, the findings could possibly be explained by impaired cytochrome oxidase activity, caused by toxic metabolites of SNP. It must be pointed out that the SNP dose used in the present study was well below the recommended maximum dose of 1.5 mg/kg (Vesey et al. 1976, Cole 1978). Tachyphylaxis was not evident.

Reductions of MAP by 30 per cent in the clinical study were not accompanied by any changes of CO. Wildsmith et al. (1973) and Khambatta et al. (1982) found that CO is unchanged or even increased when circulatory preload is maintained during SNP induced hypotension. In the present study PCW was only moderately reduced. Previous reports of an increased HR during SNP induced hypotension (Rawlinson et al. 1978, Khambatta et al. 1979, Rudehill et al. 1979) were not confirmed by this study. A diminished response to sympathetic activity occurs with increasing age (Conway et al. 1971, Kronenberg and Drage 1973, Lakatta et al. 1975), which might explain the difference between the results of previous studies and of the present one comprising several elderly patients.

Rebound hypertension after cessation of SNP administration was reported by Miller et al. (1977), Khambatta et al. (1979), and Rudehill et al. (1979). In this clinical study, cessation of SNP administration was followed by minor elevations of MAP in relation to preoperative control values. The increase of MAP may well be effects of surgical stimulation, however, and no convincing sign

of rebound hypertension was observed, neither in the clinical nor in the animal part of the study.

Effects on pulmonary function in man

In the patients pulmonary arterial pressure was significantly decreased 30 minutes after induction of hypotension with SNP but increased later on. Pulmonary vascular resistance was unchanged. A decrease in PAMP was also reported by Lagerkranser et al. (1980) and Beierholm et al. (1983). In richly hydrated patients Khambatta et al. (1982) found unchanged pulmonary haemodynamics. In dog experiments Colley and Cheney (1977) demonstrated that SNP reverses hypoxic pulmonary vasoconstriction. In the normal lung PVR is not reduced (Colley and Cheney 1977, Pearl et al. 1983). These results are confirmed by the present study.

Physiological dead space (V_D/V_T) did not increase when hypotension was induced in patients in the supine position. This agrees with the results of Khambatta et al. (1982) who investigated patients in the prone position. On the other hand, when arterial hypotension was induced in patients placed in the lateral decubitus position an increase of V_D/V_T ensued. This may occur since controlled ventilation in the lateral position causes a redistribution of the ventilation from the dependent to the non-dependent lung (Wulff and Aulin 1972). Concomitantly, the hydrostatic effects on the pulmonary circulation, in combination with the reduced PAMP, causes a reduction of the perfusion of the non-dependent lung. The ventilation-perfusion ratio of the non-dependent lung is thus increased.

Hypotension caused a decrease of arterial oxygen tension in the supine as well as in the lateral patients. This is consistent with the findings of Wildsmith et al. (1975) and Casteley et al. (1982). According to Stone et al. (1976) SNP does not increase "true" pulmonary shunting. The reduction is thus probably caused

by an increased scatter of ventilation/perfusion relationships.

Circulatory effects of halothane/N₂O anaesthesia in the rat

To obtain reference values for the effects of SNP, a study of normotensive halothane/N₂O anaesthesia was performed in rats.

In comparison with conditions in the conscious rat a significant reduction of MAP was found, while HR, CO and SVR remained essentially unchanged. The fraction of CO delivered to the brain increased, but cerebral perfusion remained unchanged. This agrees with the results of Lees et al. (1971), Smith (1973), Ahlgren et al. (1978) and Miller et al. (1980). Myocardial perfusion was maintained despite a reduction in LCW which is in contrast to findings in halothane anaesthetised dogs (Ahlgren et al. 1978). During prolonged halothane anaesthesia a very low degree of systemic a-v shunting was found, while Ahlgren et al. (1978) demonstrated increased shunting in the dog.

The most conspicuous change induced by halothane anaesthesia in the rat is the pronounced increase in hepatic arterial flow which has been reported also by Miller et al. (1980) and Ross and Daggy (1981). In dogs Andreen et al. (1977) and Ahlgren et al. (1978) found that halothane administration is accompanied by a decrease in hepatic arterial flow. The discrepancy between the results of experimental studies in rats and dogs may be species dependent.

Circulatory effects of SNP administration in the rat

No further haemodynamic changes were observed between 60 and 90 minutes of halothane/N₂O anaesthesia in the rat. Any circulatory changes following administration of SNP after 60 minutes of halothane/N₂O anaesthesia could therefore be attributed to SNP alone. When MAP was decreased by SNP by 50 per cent, CO was unchanged but HR significantly decreased. In a similar study Hoffman et al. (1982) found no change in HR. These findings are in contrast to the SNP induced increments of HR often found in young patients

(Wildsmith et al. 1973, Rudehill et al. 1979, Khambatta et al. 1979). No reason, except species dependence, can be found for the different responses of HR to SNP administration in the rat and man.

Hypotension was maintained for 15 minutes in the animal study and a small increase of the infusion rate of SNP was required to maintain MAP at an unchanged level. This implies a tendency to tachyphylaxis, possibly caused by increased renin/angiotensin release (Miller et al. 1977, Khambatta et al. 1979) and/or increased sympathetic activity (Rawlinson et al. 1978, Todd et al. 1982).

Perfusion of the spleen, small intestine and preportal area increased after the administration of SNP. A reduction of hepatic arterial flow was found which, however, was less than the increase in preportal flow, making calculated total hepatic flow significantly increased. This is in close agreement with the findings of Delaney and Miller (1979).

After withdrawal of SNP, MAP rapidly returned to control values and CO increased significantly. The perfusion of the brain, kidneys and intestine was increased in relation to control values, indicating a disturbed autoregulation of the circulation in these organs. As the half-life of SNP in the rat is only a few minutes (Höbel and Raitelhuber 1976) the results imply protracted vasodilatory effects of SNP in certain areas. Protracted effects of SNP on the cerebral circulation were reported by Auer (1978) and compromised autoregulation of the cerebral circulation by Ivanovich et al. (1976) and Turner et al. (1977).

Cardiac work as well as myocardial blood flow increased after termination of the SNP administration. This indicates an intact autoregulation of the coronary circulation.

Circulatory effects of haemorrhage during SNP infusion in the rat

Moderate blood loss during normotensive halothane anaesthesia was followed by a slight decrease in CO and significant reductions of MAP, LCW and HR occurred. Blood flow was redistributed to favour perfusion of the brain, heart, kidneys and liver at the expense of a decreased flow to the carcass. A similar circulatory response to acute blood loss has been shown in rats by Idvall (1981), and in dogs by Ericsson (1972), Ahlgren et al. (1978) and by Rosberg and Wulff (1979).

Heart rate decreased after induction of hypovolaemia. Idvall (1981) demonstrated that the conscious rat displays tachycardia when subjected to moderate haemorrhage. Castenfors and Sjöstrand (1972), however, observed that following haemorrhage in anaesthetised rats, most animals show bradycardia mediated by vagal stimulation.

Following haemorrhage during SNP induced hypotensive anaesthesia CO increased significantly, while MAP, HR and LCW were essentially unchanged. Signs of reduced systemic shunting were found in the present study as well as in the one of Rosberg and Wulff (1979).

Cerebral perfusion was non significantly increased following blood loss in the normotensive group. In the hypotensive group haemorrhage was accompanied by significant increments of the cerebral perfusion. This may be another indication of a SNP induced alteration of cerebral autoregulation.

The myocardial blood flow/LCW ratio was increased following haemorrhage in the hypotensive as well as in the normotensive group. In the former group the increase was related chiefly to increased myocardial blood flow, while in the latter group LCW was decreased. The increased ratio may constitute a compensation for a decreased arterial oxygen content (Race et al. 1967) and/or regional myocardial ischaemia (Winbury 1971, Rosberg and Wulff 1979).

In the present investigation SNP had no obvious adverse effect

on the circulatory response to acute moderate haemorrhage.

A slight metabolic acidosis was noted in both groups following haemorrhage. In the normotensive group it was probably caused by reduced peripheral tissue perfusion during hypovolaemia. In the SNP group, where CO increased, the acidosis might hypothetically be related to an accumulation of cyanide ions, caused by impaired metabolism of SNP during hypovolaemia.

CONCLUSIONS

The following conclusions can be drawn from this study:

A moderate reduction of MAP by SNP administration during halothane anaesthesia in man causes:

- a significant reduction of blood loss during THR as compared to normotensive halothane anaesthesia, NLA or epidural blockade,
- no adverse effects on postoperative blood loss,
- no untoward circulatory effects, but instead reductions of circulatory afterload and cardiac work,
- no rebound hypertension of significant degree,
- moderate metabolic changes, indicating either increased systemic a-v shunting or, possibly, toxic effects of SNP,
- no change in physiological dead space in patients in the supine position, while moderate increases in V_D/V_T ensue in patients in the lateral position.

The administration of SNP in rats during halothane anaesthesia causes

- an increased perfusion of the splanchnic organs,
- protracted vasodilation of regional areas, e.g. the brain, on withdrawal of SNP,

- maintained or even improved perfusion of vital organs after moderate haemorrhage,
- signs of impaired cerebral autoregulation during and immediately after SNP administration.

CLINICAL IMPLICATIONS

From a clinical point of view SNP induced hypotension can be recommended for cases in which major intraoperative bleeding is anticipated. This hypotensive technique is easily controlled and permits reversal of hypotension prior to wound closure in order to obtain adequate surgical haemostasis.

The favourable effects on circulatory afterload and cardiac work might make the technique an alternative also for patients with impaired cardiovascular function. It is beyond the scope of this study to discuss this in detail, but it is generally recommended to maintain arterial blood pressure at a higher level in these patients than in patients with their cardiovascular function intact. Cardiac function, arterial blood gases and acid-base variables must be carefully monitored.

Of course no absolutely valid conclusions for clinical praxis can be made from results of the experimental study. The findings of an increased perfusion of the liver implies adequate hepatic oxygenation during hypotension. The circulatory changes induced by bleeding during SNP induced hypotension imply maintained or even improved oxygenation of vital organs in this situation. Adequate replacement of blood loss should of course always be the goal. Autoregulation of cerebral blood flow is apparently compromised during and immediately after SNP administration. This should be recognised when SNP induced hypotension is considered for patients with signs of increased intracranial pressure.

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REFERENCES

- Adams, A.P., Clarke, T.N.S., Edmonds-Seal, J., Foex, P., Prys-Roberts, C. and Roberts, J. Effects of sodium nitroprusside on myocardial contractility and haemodynamics. *Br.J.Anaesth.* 1973:45:120.
- Allela, A., Williams, F., Bolene-Williams, C. and Katz, L. Interrelation between cardiac oxygen consumption and coronary blood flow. *Am. J. Physiol.* 1955:183:570.
- Ahlgren, I., Aronsen, K.F., Björkman, I. and Wetterlin, S. The hemodynamic effect of halothane in the normovolemic dog. *Acta Anaesth. Scand.* 1978:22:83.
- Ahlgren, I., Aronsen, K.F., Björkman, I. and Wetterlin, S. The effect of halothane on distribution of cardiac output and organ blood flow in the hypovolemic dog. *Acta Anaesth. Scand.* 1978:22:99.
- Andreen, M., Irestedt, L. and Zetterström B. The different responses of the hepatic arterial bed to hypovolemia and to halothane anesthesia. *Acta Anaesth. Scand.* 1977:2:457.
- Archie, J., Fixler, D., Ulliot, D., Hoffman, J., Utley, J. and Carlson, E. Measurement of cardiac output with and organ trapping of microspheres. *J. Appl. Physiol.* 1973:35:148.
- Askrog, V.F., Pender, J.W. and Eckenhoff, J.E. Changes in physiological dead space during deliberate hypotension. *Anesthesiology* 1964:25:744.
- Auer, L. The action of sodium nitroprusside on the pial vessels. *Acta Neurochirurgica* 1978:43:297.
- Baez, S., Srikanti, S.G. and Burack, B. Dibenzylamine protection against shock and preservation of hepatic ferritin system. *Am. J. Physiol.* 1958:192:175.

- Barbier-Böhm, G., Desmonts, J.M., Conderc, E., Moulin, O., Prokoci-
mer, P. and Olivier, H. Comparative effects of induced hypotension
and normovolaemic haemodilution on blood loss in total hip arthro-
plasty. *Br. J. Anaesth.* 1980;52:1039.
- Beierholm, E.A., Bredgaard-Sørensen, M., Sroczyński, Z., Spotoft,
H., Gothgen, I. and Thorshauge, C. Haemodynamic changes during
sodium nitroprusside induced hypotension and halothane/nitrous
oxide anaesthesia. *Acta Anaesth. Scand.* 1983;27:99.
- Bergman, G. and Husberg, B. A method for multiple intraarterial
injections in the allogenic or isogenic transplanted rat kidney
by use of a longterm catheter in the renal artery. *Scand. J. Urol.*
Nephrol. (Suppl.) 1980;54:116.
- Berne, R.M. Regulation of coronary blood flow. *Physiol. Rev.* 1964:
44:1.
- Brooks, C.Mc. The reaction of chronic spinal animals to hemorrhage.
Am. J. Physiol. 1935;114:30.
- Buckberg, G.D., Luck, J.C., Payne, D.B., Hoffman, J.I.E., Archie,
J.P. and Fixler, D.E. Some sources of error in measuring regional
blood flow with radioactive microspheres. *J. Appl. Physiol.* 1971:
31:598.
- Castenfors, J. and Sjöstrand, T. Circulatory control via vagal
afferents. Adjustment of heart rate to variations of blood volume
in the rat. *Acta Physiol. Scand.* 1972;84:347.
- Casthely, P.A., Lear, S., Cottrell, J.E. and Lear, E. Intrapulmonary
shunting during induced hypotension. *Anesth. Analg.* 1982;61:231.
- Coggeshall, N.O. and Saier, E.L. Pressure broadening in infrared
and optical collision diameters. *J. Chem. Phys.* 1947;15:65.
- Cohn, J.N. and Franciosa, J.A. Vasodilator therapy of cardiac failure.
N. Engl. J. Med. 1977;297:27.
- Cole, P. The safe use of sodium nitroprusside. *Anaesthesia* 1978;33:
473.

- Colley, P.S. and Cheney, F.W. Sodium nitroprusside increases Q_s/Q_t in dogs with regional atelectasis. *Anesthesiology* 1977:47:338.
- Conway, S., Wheeler, J. and Sannerstedt, R. Sympathetic nervous activity during exercise in relation to age. *Cardiovasc. Res.* 1971:5:577.
- Davison, M.H.A. Pentamethonium in anaesthesia. *Lancet* 1950:1:252.
- Davis, N.J., Jennings, J.J. and Harris, W.H. Induced hypotensive anesthesia for total hip replacement. *Clin. Orthoped.* 1974:101:93.
- Delaney, T.J. and Miller, Jr., E.D. Blood flow alterations induced by saralasin or SNP. *Anesthesiology* 1979:51:73.
- Delaney, T.J. and Miller, Jr., E.D. Rebound hypertension after SNP prevented by saralasin in rats. *Anesthesiology* 1980:52:154.
- Donald, J.R. Induced hypotension and blood loss during surgery. *R. Soc. Med.* 1982:75:149.
- Eckenhoff, J.E., Enderby, G.E.H., Larson, A., Eldridge, A. and Judevine, D.E. Pulmonary gas exchange during deliberate hypotension. *Br. J. Anaesth.* 1963:35:750.
- Edwards, Jr., M.W.E. and Fleming, D.C. Deliberate hypotension. *Clin. N. Am.* 1975:55:947.
- Enderby, G.E.H. Controlled circulation with hypotensive drugs and posture to reduce bleeding in surgery. Preliminary results with pentamethonium iodide. *Lancet* 1950:1:1145.
- Enghoff, H. Volumen inefficiax. *Uppsala Läkarreför. Förhand.*, 1938: 44:191.
- Engström, C.G. and Herzog, P. Ventilation normogram for practical use of the Engström respirator. *Acta Chir. Scand.*(Suppl.) 1959: 245:37.
- Ericsson, B.F. Early effects of haemorrhage on the distribution of cardiac output in the anesthetized dog. *Acta Chir. Scand.* 1972: 138:13.

- Fahmy, N.M. Indications and contraindications for deliberate hypotension with a review of its cardiovascular effects. *Int. Anesthesiol. Clin.* 1978:17:175.
- Fletcher, R. The single breath test for carbon dioxide. Thesis, Lund, Sweden, 1980.
- Fredin, H. Personal communication. 1983.
- Freeman, J. and Nunn, J.F. Ventilation-perfusion relationships after haemorrhage. *Clin. Sci.* 1963:24:135.
- Forrester, J.S., Ganz, W., Diamond, G., McHugh, T., Chonetta, D.W. and Swan, H.J. Thermodilution cardiac output determination with a single flow directed catheter. *Amer. Heart J.* 1972:83:306.
- Fukunga, A.F., Flacke, W.E. and Bloor, B.C. Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside infusion in the rat. *Anesth. Analg.* 1982:61:273.
- Gardner, J.W. The control of bleeding during operation by induced hypotension. *JAMA* 1946:132:572.
- Griffiths, H.W.C. and Gillies, J. Thoraco-lumbar splanchnicectomy and sympathectomy: anaesthetic procedure. *Anaesthesia* 1948:3:134.
- Gustafson, C., Ahlgren, I., Aronsen, K.F. and Rosberg, B. Haemodynamic effects of labetalol-induced hypotension in the anaesthetised dog. *Br. J. Anaesth.* 1981:53:585.
- Hamilton, W.F., Moore, J.W., Kinsman, J.M. and Spurling, R.G. Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. *Am. J. Physiol.* 1932:99:534.
- Herrman, L. The actions of sodium nitroprusside. *Arch. F. Physiol.* 1886:39:419.
- Hoffman, W.E., Satinover, I., Miletich, D.J., Albrecht, R.F. and Gans, B.J. Cardiovascular changes during SNP or ATP infusion in the rat. *Anesth. Analg.* 1982:61:99.

- Höbel, M. and Raitelhuber, A. Untersuchungen über den Stoffwechsel und die Organverteilung von ^{14}C -markiertem Natrium-nitroprusside an Ratten. *Arzneim-Forsch. (Drug.Res.)* 1976;26:2015.
- Idvall, J., Aronsen, K.F., Nilsson, L. and Nosslin, B. Evaluation of the microsphere method for determination of cardiac output and flow distribution in the rat. *Eur. Surg. Res.* 1979;11:423.
- Idvall, J. Influence of ketamin anesthesia on cardiac output and tissue perfusion in rats subjected to hemorrhage. *Anesthesiology* 1981;55:297.
- Ivankovich, A.D., Miletich, D.J., Albrecht, R.F. and Zahed, B. Sodium nitroprusside and cerebral blood flow in the anesthetised and unanesthetised goat. *Anesthesiology* 1976;44:21.
- Jacob, S., Friedman, E.W., Levenson, S., Glotzer, P., Frank, H.A. and Fine, J. Antiadrenergic and antihistaminic treatment in hemorrhagic shock in dog and man. *Am. J. Physiol.* 1956;186:79.
- Jakobson, S. and Wigren, A. Epiduralanestesi och blödning vid stor höftkirurgi. *Svensk Läkartidn.* 1972;69:267.
- Johnson, C.C. The actions and toxicity of sodium nitroprusside. *Arch. Int. Pharmacol. Ther.* 1929;35:480.
- Kaihara, S., Van Herden, P.O., Migita, T. and Wagner, Jr. H.N. Measurements of distribution of cardiac output. *J. Appl. Physiol.* 1968;25:696.
- Khambatta, H.J., Stone, J.G. and Khan, E. Hypertension during anesthesia on discontinuation of SNP induced hypotension. *Anesthesiology* 1979;51:127.
- Khambatta, H.J., Stone, J.G. and Matteo, R.S. Effect of SNP induced hypotension on pulmonary dead space. *Br. J. Anaesth.* 1982;54:1197.
- Kronenberg, R. and Drage, C.W. Attenuation of the ventilatory and the heart rate responses to hypoxia and hypercapnia with aging in normal men. *J. Clin. Invest.* 1973;52:1812.

- Lagerkranser, M., Gordon, E. and Rudehill, A. Cardiovascular effects of SNP in cerebral aneurysm surgery. *Acta Anaesth. Scand.* 1980:24:426.
- Lagerkranser, M. Controlled hypotension with sodium nitroprusside, nitroglycerine and adenosine. Thesis, Stockholm, Sweden, 1983.
- Lakatta, E., Gerstenblith, G., Agnelli, C., Shock, N.W. and Weisfeldt, M.L. Diminished inotropic response of the aged myocardium to catecholamines. *Circ. Res.* 1975:36:262.
- Lawson, N.W., Thompson, D.S., Nelson, C.L., Flacke, J.W. and North, E.R. Sodium nitroprusside induced hypotension for supine total hip replacement. *Anesth. Analg.* 1976:55:554.
- Lees, M.H., Hill, J., Ochsner, A.J. and Thomas, C. Regional blood flows of the rhesus monkey during halothane anaesthesia. *Anesth. Analg.* 1971:50:270.
- Lindop, M.J. Complications and morbidity of controlled hypotension. *Br. J. Anaesth.* 1975:47:799.
- Malik, A.B., Kaplan, J.E. and Saba, T.M. Reference sample method for cardiac output and regional blood flow determinations in the rat. *J. Appl. Physiol.* 1976:40:472.
- Malik, A.B., Loegeriz, D.J., Saba, T.M. and Kaplan, J.E. Cardiac output and regional blood flow following trauma. *Circ. Shock* 1978: 5:73.
- McDevitt, D.G. and Nies, A.S. Simultaneous measurement of cardiac output and its distribution with microspheres in the rat. *Cardiovasc. Res.* 1976:10:494.
- Mebius, C. and Hedenstierna, G. Gas exchange and respiratory mechanics during hip arthroplasty. *Acta Anaesth. Scand.* 1982: 26:15.
- Messmer, K., Stelter, W.J. and Stipping, S. Sodium nitroprusside-induced hypotension: Flow distribution and metabolism. *Eur. Surg. Res.* 1978:10:Suppl.1:51.

- Miletich, D.J. and Ivankovich, A.D. Sodium nitroprusside and cardiovascular hemodynamics. *Int. Anesth. Clin.* 1978:16:31.
- Miller, R.R., Vismara, L.A., DeMaria, A.N. Salel, A.F. and Mason, D.T. Afterload reduction therapy with nitroprusside in severe aortic regurgitation: improved cardiac performance and reduced regurgitant volume. *Am. J. Cardiol.* 1976:38:564.
- Miller, E.D., Ackerly, J.A., Vaughan, Jr.E.D., Peach, M.J. and Epstein, R.M. The renin angiotensin system during controlled hypotension with sodium nitroprusside. *Anesthesiology* 1977: 47:257.
- Miller, E.D., Kistner, J.R. and Epstein, R.M. Whole-body distribution of radioactively labelled microspheres in the rat during anesthesia with halothane, enflurane or ketamine. *Anesthesiology* 1980:52:296.
- Modig, J. and Malmberg, P. Pulmonary and circulatory reactions during hip replacement surgery. *Acta Anaesth. Scand.* 1975:19:1.
- Moraca, P.P., Ritte, E.M., Hale, D.E., Wasmuth, C.E. and Pou-tasse, E.F. Clinical evaluation of sodium nitroprusside as a hypotensive agent. *Anesthesiology* 1962:23:193.
- Mortimer, P.L.F. New apparatus for production of controlled hypotension by arteriotomy. *Anaesthesia* 1951:6:128.
- Nilsson, E. Origin and rationale of neuroleptanalgesia. *Anesthesiology* 1963:24:267.
- Nunn, J.F. and Ezi-Ashi, T.I. The accuracy of the respirometer and ventigrator. *Br. J. Anaesth.* 1962:34:422.
- Nunn, J.F. and Freeman, J. Problems of oxygenation and oxygen transport during hemorrhage. *Anaesthesia* 1964:19:206.
- Nunn, J.F. *Applied respiratory physiology with special reference to anaesthesia.* 1969: 2 nd edn. p. 231. London:Butterworths.

- Ohlsson, E.G. Regional blood flow studies with labelled microspheres of different sizes in dogs with and without occlusion of the common bile duct. *Eur. Surg. Res.* 1971:3:348.
- Page, I.H. Treatment of essential and malignant hypertension. *JAMA* 1951:147:1311.
- Pearl, R.G., Rosenthal, M.H. and Ashton, P.A. Pulmonary vasodilator effects of nitroglycerine and sodium nitroprusside in canine oleic acid-induced pulmonary hypertension. *Anesthesiology* 1983:58:514.
- Peter, K., Franke, N., Endrich, B. and Messmer, K. Microcirculatory effects of deliberately induced hypotension. *Acta Anaesth. Scand.* 1983:27 (suppl.78):60.
- Pfeffer, M.A. and Frolich, E.D. Electromagnetic flowmetry in anaesthetized rats. *J. Appl. Physiol.* 1972:33:137.
- Popovich, V.P. and Kent, K.M. 120-day study of cardiac output in unanesthetized rats. *Am. J. Physiol.* 1964:207:767.
- Race, D., Dedichen, H. and Schenk, Jr. W. Regional blood flow during dextran-induced normovolemic hemodilution in the dog. *J. Thorac. Cardiovasc. Surg.* 1967:53:578.
- Rawlinson, W.A.L., Loach, A.B. and Benedict, C.R. Changes in plasma concentration of adrenaline and noradrenaline in anaesthetised patients during sodium nitroprusside induced hypotension. *Br. J. Anaesth.* 1978:50:937.
- Rosberg, B. Acute normovolemic hemodilution. Clinical and experimental studies on hemodynamics and regional lung function. Thesis, Malmö, Sweden, 1978.
- Rosberg, B. and Wulff, K. Regional blood flow in normovolaemic and hypovolaemic haemodilution. An experimental study. *Br. J. Anaesth.* 1979:51:423.
- Ross, Jr. W.T. and Daggy, B.P. Hepatic blood flow in phenobarbital-pretreated rats during halothane anaesthesia and hypoxia. *Anesth. Analg.* 1981:60:306.

- Rudehill, A., Gordon, E. and Lagerkranser, M. Sodium nitroprusside as a hypotensive agent in intracranial aneurysm surgery. *Acta Anaesth. Scand.* 1979;23:404.
- Rudolph, A.M. and Heymann, M.A. The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circ. Res.* 1967;21:163.
- Sapirstein, L.A., Sapirstein, E.H. and Bredemeyer, A. Effect of haemorrhage on the cardiac output and its distribution in the rat. *Circ. Res.* 1960;VIII:135.
- Sasaki, Y. and Wagner, H.N. Measurements of the distribution of cardiac output in unanesthetized rats. *J. Appl. Physiol.* 1971;30:879.
- Schlossberg, T. and Sawyer, M.E.M. Studies on the homeostasis in normal, sympathectomized and ergotaminized animal. The effect of hemorrhage. *Am. J. Physiol.* 1933;104:195.
- Sculco, T.P. and Ranawat, C. The use of spinal anesthesia for total hip-replacement arthroplasty. *J. Bone Jt. Surg.* 1975;57A:173.
- Smith, A.L. The mechanism of cerebral vasodilation by halothane. *Anesthesiology* 1973;39:581.
- Stoelting, R.K., Viegas, O. and Campbell, R.L. Sodium nitroprusside produced hypotension during anesthesia and operation in the head up position. *Anesth. Analg.* 1977;56:391.
- Stone, J.G., Khambatta, H.J. and Matteo, R.S. Pulmonary shunting during anesthesia with deliberate hypotension. *Anesthesiology* 1976;45:508.
- Svedman, P. Cardiac output distribution in animals measured with radioactive dextran microspheres. Thesis, Malmö, 1977.
- Thorburn, J., Loudon, J.R. and Vallance, R. Spinal and general anaesthesia in total hip replacement. Frequency of deep vein thrombosis. *Br. J. Anaesth.* 1980;52:1117.

- Todd, M.M., Morris, P.J., Moss, J. and Philbin, D.M. Hemodynamic consequences of abrupt withdrawal of nitroprusside or nitroglycerine following induced hypotension. *Anesth. Analg.* 1982: 61:261.
- Turner, J.M., Powell, D., Gibson, R.M. and McDonald, D.G. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br. J. Anaesth.* 1977:49:419.
- Wagner, H.N., Rhodes, B.A., Sasaki, Y. and Ryan, J.P. Studies of the circulation with radioactive microspheres. *Invest. Radiol.* 1969:4:375.
- Warren, D.J. and Ledingham, J.G.G. Measurement of cardiac output distribution using microspheres. Some practical and theoretical considerations. *Cardiovasc. Res.* 1974:8:570.
- Wassén, A. The use of bromsulphthalein for determination of the cardiac output. *Scand. J. Invest.* 1956:8:189.
- Vesey, C.J. and Cole, P.V. Nitroprusside and cyanide. *Br. J. Anaesth.* 1975:47:1115.
- Vesey, C.J., Cole, P.V. and Simpson, P.J. Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. *Br. J. Anaesth.* 1976:48:651.
- Wildsmith, J.A.W., Marshall, R.L., Jenkinson, J.L., MacRae, W.R. and Scott, D.B. Haemodynamic effects of sodium nitroprusside during nitrous oxide/halothane anaesthesia. *Br. J. Anaesth.* 1973:45:71.
- Wildsmith, J.A.W., Drummond, G.B. and MacRae, W.R. Blood gas changes during induced hypotension with sodium nitroprusside. *Br. J. Anaesth.* 1975:47:1205.
- Winbury, M.M. Redistribution of left ventricular blood flow produced by nitroglycerine. *Circ. Res.* 1971:28 (suppl.1):140.

Wright, B.M. A respiratory anemometer. J. Physiol. (Lond):1955:127:35.

Wulff, K.E. and Aulin, I. The regional lung function in the lateral decubitus position during anesthesia and operation. Acta Anaesth. Scand. 1972:16:195.

Wulff, K., Arborelius Jr., M. and Rosberg, B. Regional lung function following prosthetic hip replacement surgery. Europ. J. Intensive Care Medicine 1975:1:129.

Anesthetic Techniques and Surgical Blood Loss in Total Hip Arthroplasty

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Blood loss during total hip arthroplasty and the relation of different anesthetic techniques to surgical bleeding was explored in a consecutive, prospective study involving 157 patients with no previous history of hip surgery. Intraoperative blood loss was significantly reduced in patients operated under sodium nitroprusside induced hypotensive anesthesia as compared to halothane, NLA or epidural block. It might be suspected that postoperative blood loss is increased when the lowered blood pressure is raised towards normotension, but this was not the case. However, regression analysis between mean arterial pressure and intraoperative blood loss in patients anesthetized with hypotensive as well as "normotensive" techniques showed a poor correlation. Blood loss was greater with NLA and halothane anesthesia than with epidural block. The authors consider controlled hypotension a useful adjuvant in anesthesia for total hip arthroplasty in selected patients. Epidural block, on the other hand, is a suitable anesthetic technique for most patients and has the additional advantage of reduced surgical bleeding as compared to general anesthesia.

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Total hip replacement constitutes a remarkable success in the treatment of osteoarthritis, and an increasing number of patients now undergo this operation. Mortality connected with the procedure is mainly caused by thrombo-embolism, with an incidence of 1-2% (COVENTRY *et al.* 1974, RING 1974, FREDIN & NILLIUS 1981), while intraoperative morbidity may be linked to pulmonary micro-embolization secondary to intramedullary broaching and acrylic bone-cement application (COHEN & SMITH 1971, MODIG *et al.* 1974).

Intraoperative hypovolemic shock, due to extensive blood loss and inadequate blood volume replacement, is a less frequently discussed but serious complication in these elderly patients. According to EFTEKHAR (1971), the incidence of this complication is 2-3%. The relation of different anesthetic techniques to operative blood loss has been studied, and the results suggest that hypotensive anesthesia (DAVIS *et al.* 1974, LAWSON *et al.* 1976, BARBIER-BÖHM *et al.* 1980) as well as spinal or epidural anesthesia (JAKOBSON & WIGREN 1972, SCULCO & RANAWAT 1975) might reduce operative bleeding.

The importance of the choice of anesthesia on surgical blood loss in total hip replacement was further investigated in a consecutive prospective study. Four different anesthetic techniques were used: halothane anesthesia, intentional hypotensive anesthesia, neurolept analgesia and continuous epidural analgesia.

PATIENTS AND METHODS

Two hundred consecutive patients with osteoarthritis of the hip, undergoing total hip arthroplasty, were studied. This investigation reports the data on 157 patients who had no previous history of hip surgery. Patients with no clinical and/or laboratory signs of cardiopulmonary, renal, hepatic or thyroid diseases were randomly distributed to either "normotensive" anesthesia with halothane, or intentional hypotensive anesthesia with halothane and sodium nitroprusside. The other patients in this study were operated on using either a continuous epidural block or a neuroleptic analgesic technique (NLA), according to the decision of the anesthesiologist.

All patients received thrombo-prophylaxis, with either dextran 70 (Macrodex[®], Pharmacia AB, Sweden) or a combination of heparin and dihydroergotamin (AB Sandoz, Sweden), in a randomized manner in the four groups. The Ethical Committee of the University of Lund gave its consent to this study.

Anesthesia

Controlled hypotension (group I) was used in 33 patients. Anesthesia was induced with thiopental. Succinylcholine was given intravenously to facilitate endotracheal intubation. Anesthesia was then maintained with halothane and nitrous oxide in 50% oxygen. The patients were ventilated with an Engström respirator (Engström Medical, Sweden). Arterial blood pressure was continuously monitored via an indwelling radial artery catheter (Venflon 1.2 mm, Viggo AB, Sweden). Sodium nitroprusside, 0.2 mg/ml, was infused via an infusion pump to lower the intraoperative systolic blood pressure to 70-80 mmHg. Administration of nitroprusside was started just prior to skin incision, and stopped following bone cement application in the femoral shaft.

Halothane anesthesia, induced and conducted as above but without intentional hypotension, was used in 28 patients (group II). Contin-

uous epidural block through a percutaneously inserted catheter was applied with mepivacaine 20 mg/ml with adrenalin 5 µg/ml in 79 patients (group III). The block usually reached the Th 6 level, as estimated by pin-prick. Sedation was provided with either diazepam, hexobarbital infusion or a combination of droperidol (2.5 mg) and fentanyl (0.05 mg).

A neurolept analgesic technique (NLA) was used in 17 patients (group IV). The anesthesia was induced by droperidol (10 mg), followed with inhalation of a 2:1 N₂O/O₂ mixture. Fentanyl was then slowly injected until the patient did not respond to external stimuli. Intubation was performed with an endotracheal cuffed tube after an injection of pancuronium bromide (6 mg). Additional doses of fentanyl (0.1–0.2 mg/h) were given during the operation, during which the patients were ventilated mechanically (Engström respirator, Engström Medical, Sweden). Mean arterial pressure was calculated from the formula:

$$\text{diastolic pressure} + \frac{\text{systolic pressure} - \text{diastolic pressure}}{3}$$

and registered half-way through surgery.

Intraoperative blood loss was estimated from the volume of blood in the suction apparatus, weighed sponges and drapes. Postoperative blood loss was measured from bleeding collected in suction drains.

Hemoglobin concentration was analyzed spectrophotometrically (Vitatron, AB Kistner, Sweden).

Statistical analysis

Mean values, standard deviation and standard error of the mean were calculated. Differences between the groups were evaluated by means of Student's *t*-test.

RESULTS

As shown in Table 1 and Figure 1, groups I, II and IV did not differ significantly from each other regarding age, sex distribution, hemoglobin concentration or the type of prosthesis used. However, the patients in group III (epidural anesthesia) were older.

Intraoperative blood loss was significantly ($P <$

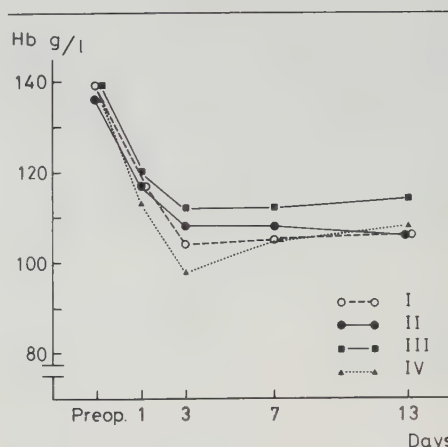


Fig. 1. Hemoglobin concentration (mean value, g/l) preoperatively and during the first 2 postoperative weeks. I = hypotensive anesthesia, II = halothane anesthesia, III = epidural analgesia and IV = NLA. The postoperative values are significantly decreased, $P < 0.001$, in all groups as compared to the preoperative ones. On the third postoperative day hemoglobin concentration in group III is significantly reduced as compared to groups I ($P < 0.05$) and IV ($P < 0.01$).

0.001) (Table 2) reduced in group I as compared to the other groups. In a comparison between patients operated with an epidural block and a normotensive general anesthesia, intraoperative blood loss was significantly ($P < 0.001$) reduced in group III as compared to group IV, while no difference between groups II and III was found.

Mean arterial pressure half-way through surgery (Table 3) was 61 ± 1.2 (mean $\pm$ s.e. mean) mmHg in the hypotensive group, significantly ($P < 0.001$) reduced as compared to the other groups. The patients in group II had a significantly ($P < 0.001$) reduced blood pressure as compared to group IV.

Regression analyses performed between mean arterial pressure half-way through surgery and intraoperative blood loss in the individual groups demonstrated a poor correlation (Fig. 2). No significant differences were found in operative time between the groups (Table 3).

Postoperative blood losses did not differ significantly between groups I, II and III, while patients undergoing hip arthroplasty in group IV had a higher postoperative blood loss as compared to group III.

Total blood loss was thus significantly reduced in group I as compared to the other groups ($P < 0.01$ I–II and I–III, $P < 0.001$ I–IV), and in group III as compared to groups II ($P < 0.05$) and IV ($P < 0.001$).

Transfusion of bank blood (Table 2) intra- and post-

Table 1

Patient data. Prosthesis 1 = Charnley, 2 = Lubinus, 3 = Harris, 4 = LeGrange le Tournel, 5 = Christiansen.

	n	Age (mean and range)	Sex	Prosthesis, n				
				1	2	3	4	5
Hypotensive anesthesia (I)	33	59 (47–85)	10 M 23 F	19	11	3		
Halothane anesthesia (II)	28	60 (32–79)	9 M 19 F	12	14	1	1	
Epidural analgesia (III)	79	69 (47–85)	25 M 54 F	39	37	1		2
NLA (IV)	17	61 (40–78)	7 M 10 F	7	9		1	

Table 2

Surgical blood loss and total bank blood transfusion (I, mean $\pm$ s.e. mean). ¹ $P < 0.001$ group I v. groups II, III and IV; ² $P < 0.001$ group III v. group IV; ³ $P < 0.05$ group III v. group IV; ⁴ $P < 0.01$ group I v. groups II and III; $P < 0.001$ v. group IV; ⁵ $P < 0.05$ group II v. group III; ⁶ $P < 0.001$ group III v. group IV; ⁷ $P < 0.05$ group I v. groups II and III; $P < 0.01$ group I v. group IV.

	Intraoperative blood loss	Postoperative blood loss	Total blood loss	Intra + postoperative transfusion
Hypotensive anesthesia (I)	0.66 $\pm$ 0.07 ¹	0.60 $\pm$ 0.11	1.27 $\pm$ 0.11 ⁴	1.12 $\pm$ 0.15 ⁷
Halothane anesthesia (II)	1.22 $\pm$ 0.13	0.74 $\pm$ 0.13	1.96 $\pm$ 0.19 ⁵	1.66 $\pm$ 0.23
Epidural analgesia (III)	1.02 $\pm$ 0.10 ²	0.58 $\pm$ 0.04 ³	1.59 $\pm$ 0.10	1.62 $\pm$ 0.10
NLA (IV)	1.78 $\pm$ 0.35	0.84 $\pm$ 0.20	2.62 $\pm$ 0.49 ⁶	2.22 $\pm$ 0.46

Table 3

Operative time (min, mean $\pm$ s.e. mean) and mean arterial pressure (MAP, mmHg, mean $\pm$ s.e. mean) half-way through surgery. ¹ $P < 0.001$ group I versus groups II, III and IV; ² $P < 0.001$ group II v. group IV.

	Operative time	MAP
Hypotensive anesthesia (I)	105 $\pm$ 4.8	61 $\pm$ 1.2 ¹
Halothane anesthesia (II)	108 $\pm$ 5.6	85 $\pm$ 2.1 ²
Epidural analgesia (III)	103 $\pm$ 3.0	92 $\pm$ 4.5
NLA (IV)	109 $\pm$ 8.0	101 $\pm$ 3.6

operatively was significantly reduced in patients operated in sodium nitroprusside induced hypotension ($P < 0.05$ I-II and I-III, $P < 0.01$ I-IV), while no significant difference in this respect was found between the other groups.

Hemoglobin concentration preoperatively and during the first 2 postoperative weeks is shown in Figure 1. Similar reductions of the measured concentrations were seen in groups I, II and III, while the postoperative anemia was more pronounced in group IV.

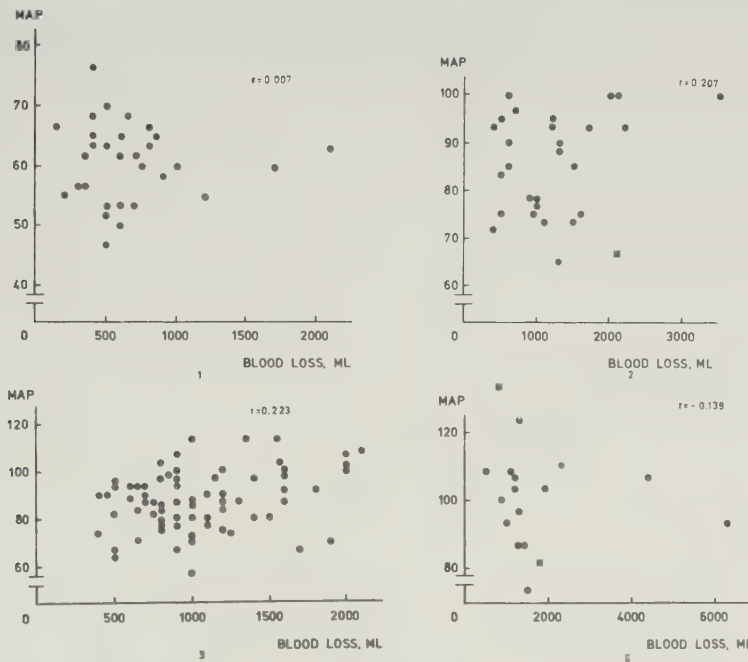


Fig. 2. Regression analyses between mean arterial pressure half-way through surgery and intraoperative blood loss. I = hypotensive anesthesia, II = halothane anesthesia, III = epidural analgesia and IV = NLA.

DISCUSSION

This prospective study analyzed the importance of different anesthetic techniques in relation to surgical blood loss in patients with no previous hip surgery. The procedure of patient distribution to the anesthesia groups merits consideration prior to discussing the results. Healthy patients, irrespective of age, were randomly distributed to general anesthesia with or without induced hypotension. Patients showing signs of systemic diseases were usually operated on with an epidural block, except for some patients in whom a neuroleptic analgesic technique was preferred. Thus the preoperative conditions of the patients in groups I and II were identical, whereas group IV and especially group III consisted of patients with concomitant systemic diseases. As shown in Table 1, the patients in group III were older than the patients in groups I and II.

Hypotensive anesthesia in this series of patients reduced intraoperative bleeding substantially. The mean blood loss, 660 ml, is in good agreement with the results of DAVIS et al. (1974), LAWSON et al. (1976) and BARBIER-BÖHM et al. (1980). The postoperative blood loss is not influenced by the hypotensive technique as compared to the other groups in this study. It has been a matter of concern (DAVIS et al. 1974) that the postoperative blood loss might be increased, thereby reducing the intraoperative effects of hypotensive anesthesia. In our study, approximately 50% of the surgical bleeding in this group was lost postoperatively. Nevertheless, the total blood loss is lower than with any other method. The use of a short-acting hypotensive agent, such as sodium nitroprusside, and the restoration of blood pressure immediately following insertion of the femoral component of the prosthesis gives the surgeon time to control bleeding vessels during wound closure. Operating time was not influenced by hypotensive anesthesia in this study, in contrast to findings by AMARANTH et al. (1975) and VAZEERY & LUNDE (1979).

Although impossible to quantify, the reduced bleeding greatly facilitated the surgeon's work. The benefits to be derived from deliberate hypotensive anesthesia are still a subject of controversy (LINDOP 1975). However, an improved understanding of the physiologic effects of this technique, and the introduction of short-acting and more easily adjustable agents like sodium nitroprusside, together with improved monitoring, have increased interest in hypotensive anesthesia, also in hip surgery (DAVIS et al. 1974, THOMPSON et al. 1978).

Epidural anesthesia reduced surgical blood loss as compared to the "normotensive" halothane and neuroleptic analgesic techniques. A beneficial effect on blood loss of epidural anesthesia has also been observed by

JAKOBSON & WIGREN (1972), but GUYOCHIN et al. (1973) could not demonstrate this. Reduced blood loss in patients undergoing hip surgery in spinal anesthesia has been reported by SCULCO & RANAWAT (1975), and recently by THORBURN et al. (1980) using a hypotensive spinal anesthesia.

Several explanations have been advanced for the decreased blood loss observed with spinal and epidural anesthesia. These techniques give a preganglionic sympathetic blockade and thus a dilatation of arteries, arterioles and veins. The resulting drop in the peripheral resistance might reduce blood pressure, but in this study no significant difference in the mean arterial pressure between epidural and normotensive general anesthesia was found. As discussed by LUND (1971), the sympathetic block gives a redistribution of blood flow, from muscle and bone to skin and subcutaneous tissues, and this may decrease blood loss during surgery around the hip joint. Also, in the dilated vessels of the lower extremity, gravity might tend to empty the non-dependent vessels, a matter of importance especially when the hip replacement is performed in the lateral position.

Controlled ventilation, used in general anesthesia in this study, gives a rise in intrathoracic (MORGAN et al. 1969) as well as venous pressure. The absence of this mode of ventilation in the epidural group may thus be another reason for the decreased bleeding as compared to the halothane and NLA groups.

The volume of transfused bank blood was significantly reduced in the hypotensive group, with a 40% reduction as compared to the "normotensive" general anesthesia groups. Despite the decreased blood loss in the epidural group, no significant reduction of bank blood transfusion was found as compared to groups II and IV. The reason for this is obvious from Table 2 and Figure 1. In the epidural group, consisting of older patients with concomitant systemic diseases, surgical blood loss was replaced as accurately as possible with bank blood.

This study focuses on the importance of the choice of anesthesia on surgical blood loss in total hip arthroplasty. Blood loss is just one and admittedly not the most important consequence of this surgical procedure, but nevertheless it is of major importance. Bank blood is a national resource available in limited amounts, and transfusion of homologous blood always carries risks of transmission of viral diseases and immunologic reactions. It is the authors' opinion that controlled hypotension, carefully monitored in selected patients, is a useful adjuvant in anesthesia for total hip arthroplasty. Epidural anesthesia, on the other hand, in addition to its few contraindications, simple technique and monitoring, also has the advantage of diminished surgical bleeding as compared to normotensive general anesthesia.

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REFERENCES

- AMARANTH, L., CASCORBI, H. F., SINGH-AMARANTH, A. V. & FRANKMANN, D. B. (1975) Relation of anesthesia to total hip replacement and control of operative blood loss. *Anesth. Analg.* **54**, 641.
- BARBIER-BÖHM, G., DESMONTS, J. M., CONDERG, E., MOULIN, O., PROKOCIMER, P. & OLIVIER, H. (1980) Comparative effects of induced hypotension and normovolaemic haemodilution on blood loss in total hip arthroplasty. *Brit. J. Anaesth.* **52**, 1039.
- COHEN, C. A. & SMITH, T. C. (1971) The intraoperative hazard of acrylic bone cement: report of a case. *Anesthesiology* **35**, 547.
- COVENTRY, M. B., BECKENBAUGH, R. D., NOLAN, D. R. & ILSTRUP, D. M. (1974) 2012 total hip arthroplasties: a study of postoperative course and early complications. *J. Bone Jt. Surg.* **56A**, 273.
- DAVIS, N. J., JENNINGS, J. J. & HARRIS, W. H. (1974) Induced hypotensive anesthesia for total hip replacement. *Clin. Orthoped.* **101**, 93.
- EFTKHAR, N. (1971) Low-friction arthroplasty. Indications, contraindications and complications. *J. Amer. med. Ass.* **218**, 705.
- FREDIN, H. & NILLIUS, S. A. (1981) Pulmonary embolism after total hip replacement. In preparation.
- GLUYCHIN, A., MAUGE, F., HARTUNG, J. & DESMONTS, J. M. (1973) Analgésie péridurale et anesthésie générale dans la chirurgie de la hanche. *Anesth. Analg.* **30**, 573.
- JAKOBSON, S. & WIGREN, A. (1972) Epiduralanestesi och blödning vid stor höftkirurgi. *Svensk. Läkartidn.* **69**, 267.
- LAWSON, N. W., THOMPSON, D. S., NELSON, C. L., FLACKE, J. W. & NORTH, E. R. (1976) Sodium nitroprusside-induced hypotension for supine total hip replacement. *Anesth. Analg.* **55**, 654.
- LINDOP, M. (1975) Complications and morbidity of controlled hypotension. *Brit. J. Anaesth.* **47**, 799.
- LUND, P. C. (1971) *Principles and practice of spinal anesthesia*. Charles C. Thomas, Springfield, Illinois.
- MODIG, J., BUSCH, C., OLERUD, S. & SALDEEN, T. (1974) Pulmonary microembolism during intramedullary orthopedic trauma. *Acta anaesth. scand.* **18**, 133.
- MORGAN, B., LUMLEY, J. & GUNTEROTH, W. (1969) The hemodynamic effects of changes in blood volume during intermittent positive pressure ventilation. *Anesthesiology* **30**, 297.
- RING, P. A. (1974) Total replacement of hip joint. *J. Bone Jt. Surg.* **56B**, 44.
- SCULCO, T. P. & RANAWAT, C. (1975) The use of spinal anesthesia for total hip-replacement arthroplasty. *J. Bone Jt. Surg.* **57A**, 173.
- THOMPSON, G. E., MILLER, R. D., STEVENS, W. C. & MURRAY, W. R. (1978) Hypotensive anesthesia for total hip arthroplasty. A study of blood loss and organ function. *Anesthesiology* **48**, 91.
- THORBURN, J., LOUDEN, J. R. & VALLANCE, R. (1980) Spinal and general anaesthesia in total hip replacement. Frequency of deep vein thrombosis. *Brit. J. Anaesth.* **52**, 1117.
- VAZEERY, A. K. & LUNDE, O. (1979) Controlled hypotension in hip joint surgery. *Acta orthop. scand.* **50**, 433.

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II

HAEMODYNAMICS AND PULMONARY DEAD SPACE DURING SODIUM
NITROPRUSSIDE INDUCED HYPOTENSION AND HIP ARHTORPLASTY

C. Gustafson and B. Rosberg

ABSTRACT

Haemodynamics and physiological dead space were studied in patients undergoing total hip arthroplasty during either sodium nitroprusside (SNP) induced hypotensive anaesthesia or normotensive anaesthesia. Surgery was performed in the lateral or the supine position.

Sodium nitroprusside, 0.12 mg/kg body weight (mean) reduced mean arterial blood pressure by 30 per cent. Cardiac output and heart rate did not change. No rebound hypertension was seen following withdrawal of SNP.

Arterial oxygen tension and pulmonary arterial pressure decreased during hypotension, while there were no significant changes in pulmonary capillary wedge pressure or vascular resistance. Physiological dead space increased only in hypotensive patients operated in the lateral position.

In the hypotensive patients a decrease in oxygen consumption, arterial pH and standard bicarbonate was found. It is hypothesised that this might depend on a SNP induced hyperkinetic circulation or, possibly, be caused by toxic metabolites from SNP, despite the very low dosage of the drug used in this study.

INTRODUCTION

Techniques to diminish the need for bank blood during surgical procedures include hypotensive anaesthesia, haemodilution and varieties of autologous blood transfusion. Of these alternatives induced hypotension has the advantage not only to reduce the risk of and the need of transfusion, but also to facilitate the surgeon's work.

The major risk of hypotensive anaesthesia is attributed to an insufficient oxygen delivery to vital organs, secondary to potentially reduced blood flow and/or disturbed arterial oxygenation. Short-acting vasodilating agents, such as sodium nitroprusside

(SNP), are usually recommended in hypotensive anaesthesia today (Lindop 1975). Sodium nitroprusside does not impair myocardial contractility (Adams et al. 1973), but reports on its effect on cardiac output are diverging (Wildsmith et al. 1973, Stoelting et al. 1977, Lagerkranser et al. 1980).

Hypotension from various causes has been shown to increase physiological dead space (V_D / V_T) and impair pulmonary gas exchange (Freeman and Nunn 1963, Eckenhooff et al. 1963, Askrog et al. 1964). In a recent study (Khambatta et al. 1982), however, it was shown that V_D / V_T did not change in patients during SNP induced hypotension, provided that their cardiac output was maintained. This study was conducted with patients in the prone position. The influence of SNP hypotension on V_D / V_T in the lateral position, which has a more pronounced hydrostatic effect on the pulmonary circulation (Nunn, 1969), has not been studied.

PATIENTS AND METHODS

Twentytwo patients with osteoarthritis of the hip, scheduled for total hip arthroplasty, were studied. They had no signs of cardiovascular, pulmonary, renal, hepatic, or thyroid diseases. All patients received thromboprophylaxis with a combination of 5 000 IU heparin and 0.5 mg dihydroergotamine (AB Sandoz, Sweden), given s.c. twice daily for ten days, starting 1 hour before surgery. They were randomly allocated into either induced hypotensive anaesthesia with halothane and sodium nitroprusside (group H), or normotensive halothane anaesthesia (group N).

In group H 6 patients (5 females and 1 male, mean age 63, range 40 - 70 years) were operated upon in the lateral position (group HL) and 6 patients (4 females and 2 males, mean age 59, range 49 - 70 years) in the supine position (group HS).

In group N 5 patients (4 females and 1 male, mean age 67, range 59 - 80 years) underwent surgery in the lateral position (group NL) and 5 patients (3 females and 2 males, mean age 60, range

37 - 80 years) in the supine position (group NS).

The investigation was approved by the Committee of Ethics, University of Lund.

Anaesthesia

The patients were premedicated with a combination of meperidine, promethazine, and atropine given i.m. one hour before anaesthesia. Patients older than 70 years received only atropine. Surgery was performed under general anaesthesia and controlled ventilation in all patients. In group H anaesthesia was induced with thiopentone. Endotracheal intubation was facilitated by i.v. succinylcholine. Anaesthesia was maintained by 0.75 - 1.5 per cent halothane and nitrous oxide in 50 per cent oxygen. No further muscle relaxant was used. SNP 0.2 mg/ml was infused via an infusion pump (Injectomat 50, Fresenius AG, FRG) to lower mean arterial pressure to 60 - 70 mm Hg. The administration of SNP was started just prior to the skin incision and stopped following completed fixation of the femoral prosthesis.

Halothane anaesthesia, induced and conducted exactly as above, but without intentional hypotension, was used in group N. During anaesthesia crystalloid fluid (Ringer-Glucos^R, ACO, Sweden), approximately $300 \text{ ml} \times \text{h}^{-1} / \text{m}^2$, was administered in both groups.

Intraoperative blood loss, estimated from the volume of blood in suction apparatus, weighed sponges, and drapes, was replaced by whole blood during surgery.

Ventilation

The patients were ventilated with an Engström 2 000 ventilator (Engström Medicals, Sweden) at a rate of 20 b.p.m. Tidal volumes were calculated according to Engström and Herzog (1959). The ventilator setting was not changed during the anaesthesia. The inspiratory/expiratory ratio was 1:2 and the square-wave flow type

was utilised. A small sized humidifier (Humid-Vent, Gibeck AB, Sweden) was used. The internal volume of the ventilator, tubings, connectors and humidifier was 1 340 ml and the compressible volume 32 ml/kPa (BTPS).

Catheterisation

A catheter (Venflon 1.2 mm, Viggo AB, Sweden) was placed percutaneously into a radial artery and a triple lumen catheter (93-1177-7 F, Edwards Lab., St Ana, Calif., USA) was inserted, guided by pressure monitoring, into the pulmonary artery, via the right internal jugular vein.

Surgical methods

Eleven patients, receiving a Lubinus' prosthesis, were operated upon in the lateral position (Robinson et al. 1980). In 11 patients surgery was performed in the supine position according to the method described by Charnley (1961). Both methods imply anchoring of the acetabular and the femoral part of the prosthesis with acrylic cement. No ventilation hole in the femoral shaft was used.

Measurements and calculations

Cardiac output ($l \times min^{-1}$) was determined using a dye dilution technique (Wassén).

Heart rate (HR,bpm) was calculated from the ECG recording.

Mean arterial pressure (MAP), pulmonary arterial mean pressure (PAMP), and pulmonary capillary wedge pressure(PCW) (mm Hg) were registered using transducers (Ailtech, Cutler & Hammer Co., Calif., USA). These were placed at midsternal level in the patients in the lateral position.

Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), $dyne \times s^{-1} \times cm^{-5}$, were calculated from the formulas:

$SVR = \frac{MAP}{CO}$ and $PVR = \frac{PAMP - PCW}{CO}$ respectively, where

MAP = mean arterial pressure, CO = cardiac output, PCW = pulmonary capillary wedge pressure.

Haemoglobin concentration ($Hb, g \times l^{-1}$) was analysed spectrophotometrically, (Vitatron, Kistner AB, Sweden).

Body temperature ($^{\circ}C$) was measured in the axilla during anaesthesia and $0.5^{\circ}C$ was added to each reading. Arterial and mixed venous blood samples were collected in heparinised glass syringes, analysed at $37^{\circ}C$ for PO_2 , PCO_2 , pH, and standard bicarbonate (IL M 113, Boston, Mass., USA), and corrected to the actual body temperature.

Oxygen content ($C_{O_2}, ml \times l^{-1}$, STPD) was calculated from the formula: $C_{O_2} = Hb \times S_{O_2} \times 1.34 + PO_2 \times 0.23$ (Nunn & Freeman 1964), where S_{O_2} denotes the saturation of the haemoglobin.

Oxygen consumption ($\dot{V}_{O_2}, ml \times min^{-1}$, STPD) was calculated as the product of CO and arterial - mixed venous oxygen content difference (Nunn & Freeman 1964).

Carbon dioxide production ($\dot{V}_{O_2}, ml \times min^{-1}$, STPD) was calculated as the product of expired minute volume and mixed expired CO_2 concentration.

Expired gas was collected from the expiratory outlet of the ventilator into a poly laminate bag (sized 100 l, Svanbergs Tekniska AB, Sweden) during a period of 2 minutes. During the collection the excess scavenging outlet was clamped. The gas volume was measured by a Wright anemometer (Wright 1955). This instrument was repeatedly checked against a spirometer (Juncalor, Grave AB, Sweden) and the difference never exceeded 4 per cent. The tidal volume was calculated by dividing the collected volume with the number of respirations.

CO₂ in expired air. The concentration of CO₂ was analysed with an infrared CO₂ analyser (Capnograph, Godard, Netherlands), calibrated against known concentrations of CO₂ in 1:1 mixtures of nitrous oxide and oxygen. Mixed expired CO₂ concentration was analysed from the contents of the bag.

Physiological dead space (including apparatus dead space) to tidal volume ratio V_D / V_T was calculated from a modified Bohr equation (Nunn 1969):

$$V_D / V_T = \frac{P_a \text{ CO}_2 - P_E^- \text{ CO}_2}{P_a \text{ CO}_2}, \text{ where } P_a \text{ CO}_2 = \text{arterial CO}_2 \text{ tension and}$$

$P_E^- \text{ CO}_2 = \text{mixed expired CO}_2 \text{ tension.}$

Procedure

Measurements of haemodynamics and collection of expired gas in group H were performed:

- I 30 minutes after induction of anaesthesia, in the lateral or supine position, respectively, before the start of surgery.
- II 30 minutes after induction of hypotension.
- III 60 minutes after induction of hypotension.
- IV 20 minutes after termination of the SNP infusion.

In group N the measurements were performed at corresponding times, but measurement III was omitted.

Statistical method

The Wilcoxon test for paired observations was used within the groups. Degrees of significance are marked as follows:

* $p \leq 0.05$, ** $p \leq 0.01$.

RESULTS

The results are presented in Tables I - V. In group H MAP decreased 30 per cent by the infusion of SNP, mean dose 0.12 mg/kg (range 0.02 - 0.38 mg/kg), during a mean operation time of 112 minutes (range 70 - 160 min). Intraoperative blood loss was 0.7 ± 0.2 l, while it was 1.3 ± 0.2 l in group N. The difference did not reach significance. Haemoglobin concentration was slightly reduced in group H, while it increased in group N. In group H CO and HR remained unchanged throughout the study. Mean arterial pressure rose above control when SNP was withdrawn. Systemic vascular resistance decreased during hypotension. Oxygen consumption and CO_2 production decreased and remained reduced 20 minutes after termination of the SNP infusion. The body temperature reduction averaged 1.1°C .

Pulmonary arterial mean pressure decreased during hypotension, while no significant changes in PCW and PVR were found. Arterial PO_2 decreased during hypotension but mixed venous PO_2 remained unchanged. Standard bicarbonate and pH decreased progressively. In group HL V_D physiol. increased during hypotension. This increase was secondary to an increase in the V_D/V_T ratio, significant at measurement II. In group HS, no significant changes in pulmonary dead space were found. In group N, CO remained unchanged, while MAP, HR, and SVR increased during surgery. No change was found in oxygen consumption or carbon dioxide production. The body temperature decreased by an average of 0.6°C . Pulmonary arterial mean pressure, PCW, and PVR remained essentially stable, while arterial PO_2 increased during the study. In group NL the increase in V_D physiol. did not reach significance. In group NS no change in pulmonary dead space was found.

TABLE I. CENTRAL HAEMODYNAMICS. INITIAL DETERMINATIONS AND CHANGES DURING TOTAL HIP ARTHROPLASTY.

Group H (hypotensive anaesthesia) n = 12, Group N (normotensive anaesthesia) n = 10.
The Wilcoxon test for paired observations is used within the groups. Degrees of significance: * $p \leq 0.05$, ** $p \leq 0.01$

	Group	I		II-I		III-I		IV-I	
		M	± SEM	M _{diff}	± SEM _{diff}	M _{diff}	± SEM _{diff}	M _{diff}	± SEM _{diff}
CO, l x min ⁻¹	H	3.0	± 0.34	+0.1	± 0.14	+0.2	± 0.36	-0.4	± 0.2
	N	3.2	± 0.32	-0.1	± 0.15			-0.1	± 0.4
HR, bpm.	H	71	± 3.3	+3	± 3.8	+4	± 2.9	+3	± 0.2
	N	66	± 2.7	+1	± 1.3			+7*	± 2.1
MAP, mm Hg	H	82	± 3.6	-25.0**	± 3.9	-22.3**	± 4.1	+8.2*	± 2.1
	N	78	± 1.6	+11.9**	± 3.0			+14.4**	± 2.7
SVR, dyne x s ⁻¹ x cm ⁻⁵	H	2453	± 260	-800**	± 181	-998*	± 267	+601*	± 210
	N	2135	± 137	+264	± 137			+303*	± 172

TABLE II. PULMONARY HAEMODYNAMICS. INITIAL DETERMINATIONS AND CHANGES DURING TOTAL HIP ARTHROPLASTY.
 Group H (hypotensive anaesthesia) $n = 12$, Group N (normotensive anaesthesia) $n = 10$.
 The Wilcoxon test for paired observations is used within the groups. Degree of significance: * $p \leq 0.05$

	Group	I		II-I		III-I		IV-I	
		M	± SEM	M _{diff}	± SEM _{diff}	M _{diff}	± SEM _{diff}	M _{diff}	± SEM _{diff}
PAMP, mm Hg	H	12.3	± 1.5	-2.8*	± 1.1	-1.4	± 1.6	+2.3	± 3.5
	N	20.6	± 1.8	-1.1	± 1.1			-0.5	± 2.2
PCW, mm Hg	H	9.1	± 1.5	-3.0	± 1.6	-2.9	± 1.9	+0.4	± 2.1
	N	15.4	± 1.8	-2.4	± 1.5			-2.1	± 2.1
PVR dyne $\times s^{-1} \times cm^{-5}$	H	94	± 12.3	-2.8	± 25.2	+35.2	± 25.5	+29.2	± 28.9
	N	150	± 34.8	+9.3	± 31.8			+29.0	± 39.2

TABLE III. OXYGEN CONSUMPTION ($\dot{V}_{O_2}$), CARBON DIOXIDE PRODUCTION ($\dot{V}_{CO_2}$), RESPIRATORY QUOTIENT (RQ), BODY TEMPERATURE AND HAEMOGLOBIN CONCENTRATION.

Initial determinations and changes during the study. Group H n = 12, Group N n = 10.

The Wilcoxon test for paired observations is used within the groups.

Degrees of significance: * $p \leq 0.05$, ** $p \leq 0.01$.

		I	II-I	III-I	IV-I
		M $\pm$ SEM	M _{diff} $\pm$ SEM _{diff}	M _{diff} $\pm$ SEM _{diff}	M _{diff} $\pm$ SEM _{diff}
$\dot{V}_{O_2}$ (STPD)					
ml $\times$ min ⁻¹ /m ²	H	83 $\pm$ 7.9	-4.8 $\pm$ 5.3	-19.3* $\pm$ 8.1	-12.4* $\pm$ 4.2
	N	75 $\pm$ 9.4	+1.7 $\pm$ 6.0		-7.0 $\pm$ 6.8
$\dot{V}_{CO_2}$ (STPD)					
ml $\times$ min ⁻¹ /m ²	H	85 $\pm$ 3.3	-10.5 $\pm$ 5.0	-8.8 $\pm$ 5.2	-10.1* $\pm$ 3.9
	N	114 $\pm$ 6.6	+4.6 $\pm$ 6.1		+4.9 $\pm$ 5.3
RQ					
$\dot{V}_{CO_2}/\dot{V}_{O_2}$	H	1.0 $\pm$ 0.1	+0.1 $\pm$ 0.1	-0.0 $\pm$ 0.0	-0.1 $\pm$ 0.1
	N	1.4 $\pm$ 0.1	-0.0 $\pm$ 0.1		-0.1 $\pm$ 0.1
BODY TEMP.					
°C	H	35.7 $\pm$ 0.3	-0.6* $\pm$ 0.2	-1.0** $\pm$ 0.2	-1.1** $\pm$ 0.3
	N	35.4 $\pm$ 0.2	-0.2 $\pm$ 0.1		-0.6** $\pm$ 0.2
Hb					
g $\times$ l ⁻¹	H	122 $\pm$ 2.8	-3.8 $\pm$ 1.6	-8.9 $\pm$ 1.6	-8.7 $\pm$ 2.0
	N	121 $\pm$ 2.8	+3.7 $\pm$ 0.9		+4.7 $\pm$ 1.0

TABLE IV. ARTERIAL BLOOD GASES, MIXED VENOUS O_2 TENSION ($p_v O_2$), AND MIXED EXPIRED CO_2 TENSION ($P_E CO_2$). Initial determinations and changes during the study.

The Wilcoxon test for paired observations is used within the groups. Degrees of significance: * $p \leq 0.05$, ** $p \leq 0.01$

	I		II-I		III-I		IV-I	
Group	M	± SEM	M _{diff}	± SEM _{diff}	M _{diff}	± SEM _{diff}	M _{diff}	± SEM _{diff}
pH	H	7.52 ± 0.01	-0.03*	± 0.01	-0.06**	± 0.01	-0.07**	± 0.02
	N	7.53 ± 0.01	-0.00	± 0.01			±0.00	± 0.01
P _a O ₂ kPa	H	20.1 ± 1.8	-4.2*	± 1.5	-2.6	± 1.9	+3.5**	± 1.0
	N	21.4 ± 2.2	+3.3*	± 1.3			+3.7**	± 1.0
p _v O ₂ kPa	H	4.6 ± 0.2	-0.2	± 0.1	+0.1	± 0.2	+0.0	± 0.3
	N	5.0 ± 0.6	-0.6	± 0.6			-0.1	± 0.4
P _a CO ₂ kPa	H	3.8 ± 0.1	+0.0	± 0.1	-0.0	± 0.1	-0.1	± 0.1
	N	3.8 ± 0.1	-0.2*	± 0.1			-0.2*	± 0.1
St bic mmol x l ⁻¹	H	22.7 ± 0.4	-1.2**	± 0.3	-2.5**	± 0.4	-3.3**	± 0.4
	N	25.6 ± 0.4	-0.4	± 0.3			-0.5	± 0.3
P _E CO ₂ kPa	H	3.0 ± 0.1	-0.0	± 0.1	-0.0	± 0.1	+0.7	± 0.1
	N	3.1 ± 0.1	-0.0	± 0.1			-0.1	± 0.1

TABLE V. PHYSIOLOGICAL DEAD SPACE (V_D PHYSIOL.), AND V_D / V_T RATIO.
 Initial determinations and changes during the study. Group HL $n = 6$,
 Group HS $n = 6$, Group NL $n = 5$ and Group NS $n = 5$.
 The Wilcoxon test for paired observations is used within the groups.
 Degree of significance: * $p \leq 0.05$.

	Group	I		II-I		III-I		IV-I	
		M	$\pm$ SEM	M_{diff}	$\pm$ SEM _{diff}	M_{diff}	$\pm$ SEM _{diff}	M_{diff}	$\pm$ SEM _{diff}
V_D PHYSIOL.	HL	198	± 13	+28*	± 9	+29*	± 11	+9	± 5
ml(BTPS)	HS	229	± 9	-5	± 11	+1	± 16	-12	± 12
	NL	244	± 19	+22	± 31			+13	± 20
	NS	219	± 15	-7	± 12			-9	± 8
V_D / V_T	HL	0.47	± 0.02	+0.09*	± 0.03	+0.07	± 0.04	+0.07	± 0.03
	HS	0.51	± 0.02	-0.01	± 0.03	+0.02	± 0.04	-0.01	± 0.02
	NL	0.49	± 0.03	-0.01	± 0.05			-0.01	± 0.04
	NS	0.43	± 0.02	-0.01	± 0.02			-0.02	± 0.01

DISCUSSION

The random allocation of this rather small number of patients into different groups yields not only a divergence in age distribution but also differences between the groups regarding the initial values. Especially when pulmonary circulation is considered, these differences are rather pronounced. As every patient serves as her own control and as the comparisons are made within the groups, the initial divergence should not influence the conclusions.

This investigation supports previous findings (Lawson et al. 1976, Barbier-Böhm et al. 1980, Rosberg et al. 1982) that deliberate hypotension during major orthopedic surgery reduces surgical blood loss, although in this study, due to the small number of patients, the difference did not reach statistical significance.

When the SNP infusion was stopped MAP rapidly rose to a level significantly above the prehypotensive value. The increased MAP might be an expression of rebound hypertension following withdrawal of SNP, secondary to increased renin-angiotensin activity (Miller et al. 1977, Khambatta et al. 1979, Rudehill et al. 1979). However, as MAP increased also in group N, effects of the surgical stimulation might still be prevalent, although mainly wound closure remained at that time. Thus, in this study, there was no definite sign of rebound hypotension.

Heart rate remained essentially stable in both groups during surgery. Hypotension induced by SNP, per se, is known to increase sympathetic activity (Rawlinson et al. 1978, Todd et al. 1982). The stable heart rate, registered in our hypotensive patients, may be explained by experimental and clinical studies (Conway et al. 1973, Lakatta et al. 1975) indicating a diminished intrinsic response to catecholamines with increasing age.

Cardiac output was unchanged in both groups. The effect of SNP on CO in different studies is diverging (Adams et al. 1973,

Wildsmith et al. 1973, Khambatta et al. 1979, Lagerkranser et al. 1980). This variance might be secondary to factors like age and anaesthetic technique, but as SNP does not affect myocardial contractility (Adams et al. 1973), CO is primarily depending on the balance between preload and afterload. In this study the unaffected CO is related to a maintained preload and a significant reduction in afterload.

Total oxygen consumption decreased during hypotension and remained reduced 20 minutes after the withdrawal of SNP. This decrease averaged 20 per cent, and ran parallel with a reduction in the carbon dioxide production. The reduction in oxygen consumption was also concomitant with a progressive decrease in arterial pH and standard bicarbonate. None of these changes were found in group N. A diminished oxygen consumption is well known during hypothermia (Halkola et al. 1972). Lawson et al. (1976) reported a significant and troublesome temperature loss during nitroprusside hypotension in an operating room with laminar air flow. Temperature losses were evident also in the present study, but the difference between the hypotensive and the normotensive groups was small, 0.5°C , and should not account for this metabolic divergence. The reduced oxygen consumption may be explained by hyperkinetic circulation induced by SNP. Experimental studies have revealed that SNP increases arterio-venous shunting in the skeletal muscle (Messmer et al. 1978, Peter et al. 1983). Another explanation could be that the cellular cytochrome oxidase activity is impaired by the metabolites of SNP, thereby causing tissue hypoxia (Fahmy et al. 1979). The SNP dose used in this study however, 0.12 mg/kg (range $0.02 - 0.38 \text{ mg/kg}$), was well below the recommended maximum dose, 1.5 mg/kg (Vesey et al. 1976, Cole 1978).

Pulmonary arterial mean pressure decreased during hypotension in agreement with previous studies (Lagerkranser et al. 1980, Beierholm et al. 1983), while there were no significant changes in PCW and PVR. Khambatta et al. (1982) on the other hand, reported main-

tained PAMP, during SNP induced hypotension.

Pulmonary circulation in group N was unaffected.

Arterial PO_2 decreased in group H, but returned to the previous value when SNP was withdrawn. This supports the findings of Wildsmith et al. (1975) and Casthely et al. (1982) suggesting that the reduction in P_aO_2 is caused by an increased scatter of ventilation/perfusion relationships during SNP induced hypotension.

In the present investigation, physiological dead space calculations include dead space of the ventilation system. No correction was made for the variance in external dead space, 32 ml/kPa, consisting mainly of compressed gas. In this study no detailed measurements of airway pressure were made. Mebius and Hedenstierna (1982) reported raised end inspiratory pressures, mean increase 0.27 kPa, during the course of total hip arthroplasty. In our study, this would correspond to an increased external dead space of approximately 9 ml.

In group NL no significant changes in dead space were found during the study. This finding agrees with the result of Wulff and Aulin (1972). They demonstrated that the start of controlled ventilation in the lateral position immediately reduces ventilation of the dependent lung. They reported no further changes during 1 to 2 hours of inhalation anaesthesia with halothane-nitrous oxide during a minor surgical trauma. Hip arthroplasty, constituting a substantial musculo-skeletal trauma, has been shown to induce transient pulmonary dysfunction (Modig and Malmberg 1975, Wulff et al. 1975, Mebius and Hedenstierna 1982). Obviously this influence was too small to significantly change the dead space in the normotensive patients in this study.

When systemic arterial pressure, and also pulmonary arterial pressure, were reduced in the lateral position (group HL), physiological dead space increased significantly. Controlled ventilation in the lateral position redistributes ventilation from the

lower to the upper lung. These pulmonary effects are probably augmented by a decreased perfusion of the better ventilated lung, caused by reduced pulmonary arterial pressure, although total pulmonary blood flow is maintained. Thus the mechanism is probably similar to that observed by Eckenhoff et al. (1963) regarding the increase in dead space during head-up tilt and deliberate hypotension.

No changes were found in dead space in group NS. This finding agrees with the results of Modig and Malmberg (1975). Mebius and Hedenstierna (1982), on the other hand, reported a slightly increased anatomical dead space in this position during hip arthroplasty, probably caused by an increased airway pressure.

Pulmonary dead space was unchanged also in the hypotensive supine patients, in accordance with the results of Khambatta et al. (1982) in their study of patients in the prone position during nitroprusside hypotension. Probably reduced pulmonary arterial pressure increases areas within the lungs with a high ventilation/perfusion ratio, as suggested by a reduced arterial oxygen tension, also in the supine position.

In conclusion, sodium nitroprusside induced hypotension is a useful tool for reducing surgical blood loss during major surgery. The metabolic changes found during hypotension imply that arterial blood gases should be followed to reveal metabolic acidosis. Arterial hypoxaemia, caused by increased ventilation/perfusion scattering, should be counteracted by a high inspiratory oxygen concentration. When SNP hypotension is induced in patients in the lateral position, there is an increase in physiological dead space.

REFERENCES

- Adams A P, Clarke T N S, Edmonds-Seal J, Foex P, Prys-Roberts C, Roberts J. Effects of SNP on myocardial contractility and haemodynamics. *Br J Anaesth* 1973;45:120.
- Askrog V F, Pender J W, Eckenhoff J E. Changes in physiological dead space during deliberate hypotension. *Anesthesiology* 1964; 25:744.
- Barbier-Böhm G, Desmonts J M, Conderc E, Moulin O, Prokocimer P, Olivier H. Comparative effects of induced hypotension and normovolaemic haemodilution on blood loss in total hip arthroplasty. *Br J Anaesth* 1980;52:1039.
- Beierholm E A, Bredgaard-Sorensen M, Sroczyński Z, Spotoft H, Gothgen I, Thorshauge C. Haemodynamic changes during sodium nitroprusside induced hypotension and halothane/nitrous oxide anaesthesia. *Acta Anaesth Scand* 1983;27:99.
- Casthely P A, Lear S, Cottrell J E, Lear E. Intrapulmonary shunting during induced hypotension. *Anesth Analg* 1982;61:231.
- Charnley J. Arthroplasty of the hip. A new operation. *Lancet* 1961; i:1129.
- Cole P. The safe use of sodium nitroprusside. *Anaesthesia* 1978;33: 473.
- Conway S, Wheeler J, Sannerstedt R. Sympathetic nervous activity during exercise in relation to age. *Cardiovasc Res* 1971;5:577.
- Eckenhoff J E, Enderby G E H, Larson A, Eldridge A, Judevine D E. Pulmonary gas exchange during deliberate hypotension. *Br J Anaesth* 1963;35:750.
- Engström C G, Herzog P. Ventilation normogram for practical use of the Engström respirator. *Acta Chir Scand (suppl)* 1959;245:37.
- Fahmy N R, Roberts J T, Lappas D G. Nitroprusside induced hypo-

tension: Role of heart rate in determining haemodynamic effects and tachyphylaxis. *Anesthesiology* 1979;51:S 71.

Freeman J, Nunn J F. Ventilation-perfusion relationships after haemorrhage. *Clin Sci* 1963;24:135.

Halkola L, Koivikko A, Länsimies A. Haemodynamic responses of relaxed, β -blocked, and shivering dogs during hypothermia. *Acta Physiol Scand* 1972;85:212.

Khambatta H J, Stone J G, Kahn E. Hypertension during anaesthesia on discontinuation of SNP induced hypotension. *Anesthesiology* 1979;51:127.

Khambatta H J, Stone J G, Matteo R S. Effect of SNP induced hypotension on pulmonary dead space. *Br J Anaesth* 1982;54:1197.

Kronenberg R, Drage C W. Attenuation of the ventilatory and the heart rate responses to hypoxia and hypercapnia with aging in normal men. *J Clin Invest* 1973;52:1812.

Lagerkranser M, Gordon E, Rudehill A. Cardiovascular effects of sodium nitroprusside in cerebral aneurysm surgery. *Acta Anaesth Scand* 1980;24:426.

Lakatta E, Gerstenblith G, Agnelli C, Shock N W, Weisfeldt M L. Diminished inotropic response of the aged myocardium to catecholamines. *Circulat Res* 1975;36:262.

Lawson N W, Thompson D S, Nelson C L, Flacke J W and North E R. Sodium nitroprusside induced hypotension for supine total hip replacement. *Anesth Analg* 1976;26:327.

Lindop M J. Complications and morbidity of controlled hypotension. *Br J Anaesth* 1975;47:799.

Mebius C, Hedenstierna G. Gas exchange and respiratory mechanics during hip arthroplasty. *Acta Anaesth Scand* 1982;26:15.

Messmer K, Stelter W J, Stipping S. Sodium nitroprusside-induced

- hypotension. Flow distribution and metabolism. *Europ Surg Res* 1978: 10:Suppl.1:51.
- Miller E D, Ackerly J A, Vaughan Jr E D, Peach M J, Epstein R M. The renin-angiotensin system during controlled hypotension with SNP. *Anesthesiology* 1977:47:257.
- Modig J, Malmberg P. Pulmonary and circulatory reactions during hip replacement surgery. *Acta Anaesth Scand* 1975:19:1.
- Nunn J F, Freeman J. Problems of oxygenation and oxygen transport during haemorrhage. *Anaesthesia* 1964:19:206.
- Nunn J F. Applied respiratory physiology with special reference to anaesthesia. 1969: 2nd edn:p.231. London: Butterworths.
- Peter K, Franke N, Endrich B, Messmer K. Microcirculatory effects of deliberately induced hypotension. *Acta Anaesth Scand* 1983:27: (suppl 78):60.
- Rawlinson W A L, Loach A B, Benedict C R. Changes in plasma concentration of adrenaline and noradrenaline in anaesthetised patients during sodium nitroprusside induced hypotension. *Br J Anaesth* 1978:50:937.
- Robinson R P, Robinson H J, Salvati E A. Comparison of the trans-trochanteric and the posterior approaches for total hip arthroplasty. *Clin Orthop* 1980:147:143.
- Rosberg B, Fredin H, Gustafson C. Anaesthetic techniques and surgical blood loss in total hip arthroplasty. *Acta Anaesth Scand* 1982:26:189.
- Rudehill A, Gordon E, Lagerkranser M. Sodium nitroprusside as a hypotensive agent in intracranial aneurysm surgery. *Acta Anaesth Scand* 1979:23:404.
- Stoelting R K, Viegas O, Campbell R L. Sodium nitroprusside produced hypotension in the head-up position. *Anesth Analg* 1977:56: 391.

- Todd M M, Morris P J, Moss J, Philbin D M. Hemodynamic consequences of abrupt withdrawal of nitroprusside or nitroglycerine following induced hypotension. *Anesth Analg* 1982;61:261.
- Wassén A. The use of bromsulphthalein for determination of the cardiac output. *Scand J Invest* 1956;8:189.
- Vesey C J, Cole P V, Simpson P J. Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. *Br J Anaesth* 1976 :48:651.
- Wildsmith J A W, Marshall R L, Jenkinson J L, MacRae W R, Scott D B. Haemodynamic effects of sodium nitroprusside during nitrous oxide /halothane anaesthesia. *Br J Anaesth* 1973;45:71.
- Wildsmith J A W, Drummond G B, MacRae W R. Blood gas changes during induced hypotension with sodium nitroprusside. *Br J Anaesth* 1975;47:1205.
- Wright B M. A respiratory anemometer. *J Physiol (Lond)* 1955;127:35.
- Wulff K E, Aulin I. The regional lung function in the lateral decubitus position during anesthesia and operation. *Acta Anaesth Scand* 1972;16:195.
- Wulff K, Arborelius Jr M, Rosberg B. Regional lung function following prosthetic hip replacement surgery. *Europ J Intensive Care Medicine* 1975;1:129.

III

CENTRAL HAEMODYNAMICS AND REGIONAL BLOOD FLOW DURING
HALOTHANE - NITROUS OXIDE ANAESTHESIA AND CONTROLLED
VENTILATION.

C. Gustafson, K.F. Aronsen, J. Idvall and B. Rosberg

ABSTRACT

The haemodynamic effects of halothane - N_2O/O_2 anaesthesia with controlled ventilation were studied in rats, using the microsphere method. Mean arterial blood pressure was significantly reduced but only minor effects on cardiac output (CO), heart rate, and systemic vascular resistance were seen. During anaesthesia, there were significantly increased fractions of CO delivered to brain and liver (hepatic artery), while the fractions to spleen, stomach and carcass were decreased. Fractional distribution and regional blood flow to heart, kidneys, adrenals and preportal area remained unchanged. When anaesthesia was prolonged from 60 to 90 minutes, no further changes in central or regional haemodynamics were seen.

Considering the minor effects on central haemodynamics and the absence of changes in central and regional haemodynamics at 60 and 90 minutes, this anaesthesia model should be useful in experimental research.

INTRODUCTION

The haemodynamic effects of halothane are well documented in man (7,15,19) and larger animals (1,2,11,12). However, rats are used to an increasing extent in experimental work, as they are homogeneous and inexpensive.

A modification of the microsphere technique for studies of regional blood flow (17) has proved valid for investigations in rats (9,22).

Using the microsphere method, Miller et al. (1980) and Ross and Daggy (1981) have studied haemodynamics in rats during halothane anaesthesia and spontaneous breathing of oxygen or room air. In clinical anaesthesia however, controlled ventilation with halothane in a nitrous oxide/oxygen mixture is more commonly used. No information seems to be available concerning the haemodynamic effects of this technique in rats.

The aim of this investigation was to determine the central and regional haemodynamic effects induced by prolonged halothane, nitrous oxide/oxygen anaesthesia, during controlled ventilation and thereby establish an anaesthesia model for the rat.

MATERIAL AND METHODS

Sixteen male Wistar rats, weight 229 g (range 180-345 g) were studied. The animals were purebred, pathogen-free, aged 3-5 months and supplied by Møllegaard Breeding laboratory (Copenhagen, Denmark). Prior to the experiments they were kept 4 in each littered cage, sized 0.24 m^2 , with pellets ad lib and water from a drinking bottle. In 10 animals (group 1) haemodynamic measurements were done in the conscious state, and then repeated after 60 minutes of halothane anaesthesia, while in six animals (group 2), measurements were performed after 60 and 90 minutes of anaesthesia. The investigation was approved by the Regional Committee of Ethics in Animal Experiments.

Preparation of the animals

The rats in group 1 had catheters placed during ether anaesthesia. Using a metal stylet (18), a specially prepared polyethylene catheter (PE 10) was inserted into the left ventricle of the heart via the right carotid artery. A PE 90 catheter with its tip tapered for 40 mm was introduced into the abdominal aorta via one of the femoral arteries. The catheters were drawn subcutaneously, retrieved via a neck incision, protected with a hard plastic tube, flushed with heparinised saline, and clamped. The rat was left to recover for 12 to 24 hours in a special cage (5), which allowed free movement and access to water and pellets. After haemodynamic measurements in the conscious animals, these were anaesthetised with halothane in a nitrous oxide/oxygen mixture and their tracheas cannulated.

Preparation of the rats in group 2 was done during halothane

anaesthesia just prior to the experiment. No additional local anaesthesia was used. All volume losses due to blood samples were compensated by a 3-fold volume of saline.

After experiment completion the anaesthetised animals were killed by an injection of air in the heart catheter, and the correct position of this catheter was checked by necropsy.

Anaesthetic technique

Prior to the investigation the lowest concentration of halothane, which together with 60 per cent nitrous oxide in oxygen gave loss of the corneal and righting reflexes was found to be 1 per cent. A gas mixture of 1 per cent halothane and 60 per cent nitrous oxide in oxygen was prepared in a reservoir bag using a Fluotec Mark 2 vaporiser (Cyprane Ltd., Buffalo, N.Y). The gas mixture was delivered to the rats via a small animals ventilator (Braun AG, Melsungen, Germany). Ventilation rate was fixed at 80 min^{-1} and tidal volume adjusted to keep an arterial PCO_2 of approximately 4.0 kPa. The ventilator settings were not changed during the experiment. The delivered halothane concentration was repeatedly measured spectrophotometrically (EMMA, Engström Medicals, Sweden) and found to remain constant.

The body temperature of the animals was kept around 37°C , using a warming lamp.

Blood pressure was continuously monitored using a transducer (EMT 734, Siemens Elema, Sweden) connected to the aortal catheter.

The heart rate was calculated from the pressure recordings.

Arterial blood samples were analysed for pH, PCO_2 , PO_2 and standard bicarbonate, using 0.5 ml of blood (ABL 1, Radiometer, Denmark).

Haematocrit was determined in duplicate, using $20 \mu\text{l}$ of blood. The heparinised microtubes were centrifuged at $1\,000 \text{ g}$ for 10 minutes.

Systemic vascular resistance (SVR, $\text{mm Hg} \times \text{ml}^{-1} \times \text{min}$) was derived

from the formula $SVR = \frac{MAP}{CO}$, where MAP = mean arterial pressure and CO = cardiac output.

Left cardiac work (LCW, mm Hg x ml x min⁻¹) was calculated from the formula $LCW = MAP \times CO$.

Microspheres type NEN-TRAC (NEN Co, New England, USA) of 15 ± 1 (SD) μ m diameter and labelled with ⁴⁶Sc or ¹⁰³Ru were used. Approximately $1-2 \times 10^5$ spheres were injected into the left ventricle during a 3 - 5 second period.

Cardiac output was determined by the reference sample method (3,9). Blood was withdrawn from the aortal catheter at a rate of $0.6 \text{ ml} \times \text{min}^{-1}$ for 30 seconds using a withdrawal pump (model 351, Sage Instruments, Cambridge, Mass., USA). Cardiac output was calculated using the formula $CO = Q_r \frac{I_t F}{I_r}$ where CO = cardiac output, Q_r = withdrawal rate ($0.6 \text{ ml} \times \text{min}^{-1}$), I_t = total injected radioactivity and I_r = radioactivity of the reference sample. F is a conversion factor necessary as I_t and I_r are obtained by two different gamma spectrometers.

Regional blood flow. Total amount of injected activity was determined by measuring the whole rat in a lead-shielded detector. The detector was connected to a gamma spectrometer (Canberra Model 818) with window settings at 450-550 keV (¹⁰³Ru) and 700-1 000 keV (⁴⁶Sc). Animal standards were used to correct for overlapping of the isotopes. The organs were removed, weighed, and put in small plastic tubes. Large organs were divided. The inner lining of the left ventricle of the heart and the valvular cusps were excised to obtain a correct value of myocardial blood flow (9).

Concentrated sulphuric acid was added to homogenise the tissues and to produce identical volumes, in order to minimise geometrical error. The activity of specimens was determined in an automatic well counter (2x2 inch well crystal, Nuclear Chicago) connected to a gamma spectrometer (Ultrascaler 2, Nuclear Chicago). Standard

solutions of the isotopes were used to correct for isotope overlapping. Carcass activity was determined in the scintillation detector after organ removal.

Experimental protocol. In each rat cardiac output and regional blood flow were measured twice. The spheres in the first injection were labelled with ^{46}Sc , while those in the second injection were labelled with ^{103}Ru . At the same points of time arterial blood gases and haematocrit were determined.

Statistical method. The Wilcoxon test for paired observations was used. Degrees of significance are marked as follows:

* $p \leq 0.05$ ** $p \leq 0.01$

RESULTS

The injection of microspheres was well tolerated and no arrhythmia was observed in the animals studied. Haematocrit values were essentially stable during the study.

Halothane - N_2O - O_2 anaesthesia and controlled ventilation.

Central haemodynamic data are presented in Table I. Mean arterial blood pressure was significantly decreased after one hour of anaesthesia. There were no significant reductions in cardiac output (CO), heart rate, systemic vascular resistance or left cardiac work. There was no sign of acidosis or other change in the arterial blood gas analysis.

The fractional distribution of CO and regional blood flow (Table II) to heart, kidneys, adrenals, large intestine and preportal area were unchanged. Significantly increased fractions of CO were delivered to brain and liver (hepatic artery) during anaesthesia. Hepatic arterial flow was also significantly increased, while the absolute blood flow to brain, lungs and small intestine remained unchanged. During anaesthesia the fractional distribution of CO and the absolute perfusion of spleen and stomach were significant-

Table I. Physiological data for group 1, conscious and after 60 minutes of halothane anaesthesia (MEAN + SEM).

The Wilcoxon test for paired observations was used within the groups. Degree of significance: * $p \leq 0.05$ ** $p \leq 0.01$

	Conscious	60 min of anaesthesia
MAP mean arterial pressure, mm Hg	116 ± 4	$93 \pm 7^{**}$
HR heart rate, min^{-1}	423 ± 19	414 ± 13
CO/kg cardiac output $\times \text{kg}^{-1}$, $\text{ml} \times \text{kg}^{-1} \times \text{min}^{-1}$	391 ± 40	322 ± 37
SVR systemic vascular resistance, $\text{mm Hg} \times \text{ml}^{-1} \times \text{min}$	1.7 ± 0.4	1.6 ± 0.3
LCW left cardiac work $\text{mm Hg} \times \text{ml} \times \text{min}^{-1}$	9362 ± 974	6552 ± 992
ARTERIAL BLOOD GASES:		
pH	7.35 ± 0.02	7.36 ± 0.05
PCO_2 , kPa	4.0 ± 0.4	3.9 ± 0.3
PO_2 , kPa	18.2 ± 0.8	18.3 ± 0.7
st bic, $\text{mmol} \times \text{l}^{-1}$	18.7 ± 1.3	18.6 ± 2.7
HAEMATOCRIT, %	41 ± 1.4	$38 \pm 1.4^*$

Table II. Fractional distribution of cardiac output and individual organ blood flow in group 1, conscious and after 60 minutes of anaesthesia (MEAN $\pm$ SEM).

The Wilcoxon test for paired observations was used within the groups. Degree of significance: * $p \leq 0.05$ ** $p \leq 0.01$

	Conscious		60 min of anaesthesia	
	Fraction %	Flow ml $\times$ g ⁻¹ $\times$ min ⁻¹	Fraction %	Flow ml $\times$ g ⁻¹ $\times$ min ⁻¹
Brain	2.8 $\pm$ 0.2	1.4 $\pm$ 0.2	4.0 $\pm$ 0.4**	1.6 $\pm$ 0.3
Heart	3.8 $\pm$ 0.5	5.5 $\pm$ 1.1	4.3 $\pm$ 0.3	4.3 $\pm$ 0.3
Lungs	1.1 $\pm$ 0.3	0.7 $\pm$ 0.2	1.3 $\pm$ 0.5	0.8 $\pm$ 0.3
Kidneys	10.5 $\pm$ 0.7	4.1 $\pm$ 0.5	11.9 $\pm$ 0.7	3.7 $\pm$ 0.4
Spleen	1.6 $\pm$ 0.1	2.3 $\pm$ 0.3	0.8 $\pm$ 0.1**	1.0 $\pm$ 0.2**
Stomach	2.0 $\pm$ 0.2	1.3 $\pm$ 0.2	1.5 $\pm$ 0.2*	0.8 $\pm$ 0.1*
Small intest.	12.4 $\pm$ 0.8	2.1 $\pm$ 0.2	11.7 $\pm$ 0.5	1.7 $\pm$ 0.2
Large intest.	4.0 $\pm$ 0.3	1.6 $\pm$ 0.2	4.3 $\pm$ 0.3	1.5 $\pm$ 0.3
Liver (hepatic artery)	1.5 $\pm$ 0.3	0.1 $\pm$ 0.03	8.3 $\pm$ 0.8**	0.5 $\pm$ 0.09**
Adrenal glands		3.8 $\pm$ 0.6		3.1 $\pm$ 0.5
Preportal area	15.9 $\pm$ 0.3		14.0 $\pm$ 0.6	
Carcass	56 $\pm$ 2		48 $\pm$ 2**	

Table III. Physiological data for group 2; measurements after 60 and 90 minutes of halothane anaesthesia (MEAN $\pm$ SEM).

The Wilcoxon test for paired observations was used. Degree of significance:

* $p \leq 0.05$.

	60 minutes of anaesthesia	90 minutes of anaesthesia
MAP mean arterial pressure, mm Hg	99 $\pm$ 7	98 $\pm$ 6
HR heart rate, min ⁻¹	427 $\pm$ 6	428 $\pm$ 5
CO cardiac output $\times$ kg ⁻¹ , ml $\times$ kg ⁻¹ $\times$ min ⁻¹	262 $\pm$ 34	279 $\pm$ 22
SVR systemic vascular resistance, mm Hg $\times$ ml ⁻¹ $\times$ min	1.8 $\pm$ 0.4	1.6 $\pm$ 0.3
LCW, left cardiac work, mm Hg $\times$ ml $\times$ min ⁻¹	6514 $\pm$ 1056	7346 $\pm$ 1445
ARTERIAL BLOOD GASES:		
pH	7.41 $\pm$ 0.03	7.43 $\pm$ 0.02
PCO ₂ , kPa	4.1 $\pm$ 0.3	4.0 $\pm$ 0.3
PO ₂ , kPa	20.4 $\pm$ 1.3	20.2 $\pm$ 1.3
st bic, mmol $\times$ l ⁻¹	20.4 $\pm$ 1.3	21.4 $\pm$ 1.5
HAEMATOCRIT, %	43 $\pm$ 0.4	41 $\pm$ 0.5*

Table IV. Fractional distribution of cardiac output and individual organ blood flow in group 2; measurements taken after 60 and 90 minutes of halothane anaesthesia (MEAN $\pm$ SEM).

	60 min of anaesthesia			90 min of anaesthesia		
	Fraction %	Flow ml $\times$ g ⁻¹ $\times$ min ⁻¹		Fraction %	Flow ml $\times$ g ⁻¹ $\times$ min ⁻¹	
Brain	3.1 $\pm$ 0.4	1.0 $\pm$ 0.1		3.2 $\pm$ 0.3	1.1 $\pm$ 0.2	
Heart	3.9 $\pm$ 0.5	3.6 $\pm$ 0.6		4.4 $\pm$ 0.6	4.5 $\pm$ 0.8	
Lungs	1.7 $\pm$ 0.3	0.6 $\pm$ 0.1		1.4 $\pm$ 0.3	0.5 $\pm$ 0.1	
Kidneys	10.3 $\pm$ 0.7	2.6 $\pm$ 0.2		11.9 $\pm$ 0.9	3.5 $\pm$ 0.4	
Spleen	0.8 $\pm$ 0.2	0.9 $\pm$ 0.1		0.7 $\pm$ 0.1	0.8 $\pm$ 0.2	
Stomach	1.1 $\pm$ 0.1	0.5 $\pm$ 0.1		1.3 $\pm$ 0.1	0.6 $\pm$ 0.1	
Small intest.	9.0 $\pm$ 0.7	1.1 $\pm$ 0.2		9.8 $\pm$ 0.3	1.3 $\pm$ 0.2	
Large intest.	4.0 $\pm$ 0.3	1.2 $\pm$ 0.2		4.2 $\pm$ 0.3	1.5 $\pm$ 0.3	
Liver (hepatic artery)	7.1 $\pm$ 0.7	0.4 $\pm$ 0.06		7.2 $\pm$ 0.7	0.4 $\pm$ 0.05	
Adrenal glands		5.3 $\pm$ 1.2			4.9 $\pm$ 1.4	
Preportal area	10.9 $\pm$ 0.6			12.0 $\pm$ 0.4		
Carcass	55 $\pm$ 2			54 $\pm$ 2		

ly reduced.

Carcass received a significantly lower fraction of CO during anaesthesia as compared to the conscious state.

Influence of prolonged halothane - N_2O - O_2 anaesthesia and artificial ventilation.

Haemodynamic measurements after 60 and 90 minutes of anaesthesia are shown in Table III and IV. No changes in central haemodynamics, arterial blood gases, fractional distribution of CO, or regional blood flow were observed during this period.

DISCUSSION

The injections of microspheres did not cause cardiac arrhythmia or change in systemic arterial pressure. It has been shown from our laboratory (9,22) that repeated injections of large amounts of 15 μ m spheres, 1×10^4 and 4.5×10^5 respectively, do not disturb peripheral circulation in the rat.

To resemble clinical anaesthesia, halothane, nitrous oxide in oxygen, and controlled ventilation were chosen for the anaesthesia model. Repeated measurements during the experiment demonstrated stable halothane concentrations. Duncan and Raventos (1959) found that inhalation of 1.5 per cent halothane results in a rapid rise in concentration of anaesthetic in blood, and that equilibrium is reached within one hour. The measurements in this investigation were performed after 60 and 90 minutes to see whether also central and regional haemodynamics remained steady during prolonged anaesthesia.

Halothane per se induces myocardial depression and ganglionic blockade (14), but there have been reports on endogenic catecholamine release during general anaesthesia and surgical trauma, partly counteracting these effects (8). Bahlman et al. (1971) have shown that nitrous oxide plus halothane produce less depression on myocardial function, cardiac output and mean arterial pressure in man,

than does halothane alone at the same minimum alveolar concentration (MAC).

In the present investigation MAP was significantly reduced by anaesthesia whereas heart rate remained unchanged. The reduction in MAP should not be caused by hypovolaemia, as blood withdrawn for analysis was replaced by a 3-fold volume of saline. In the conscious rat mean cardiac output was 391 ml/kg, as compared to 322 ml/kg during anaesthesia. The value for conscious animals agrees with the findings of Miller et al. (1980). However, in that investigation, like in one by Ross and Daggy (1981), cardiac output was significantly reduced by halothane anaesthesia. In neither of those two studies nitrous oxide was used. In the present investigation one might expect cardiac output to be reduced by the combination of halothane and controlled ventilation, especially as normocapnia was maintained. The divergent results could be explained by the sympathomimetic effects of nitrous oxide (4,20). Although there was a significant reduction in MAP, systemic vascular resistance did not change during anaesthesia. This agrees with the findings of Ahlgren et al. (1978), Miller et al. (1980) and Prys-Roberts (1980).

The fraction of CO delivered to the brain increased during anaesthesia, although no change in absolute brain perfusion was registered. Halothane is known to dilate the cerebral vessels (21), and the findings agree with those of Lees et al. (1971), Ahlgren et al. (1978), and Miller et al. (1980).

The distribution of microspheres to the lungs comprises blood flow to the bronchial arteries and peripheral a-v shunting. Kaihara et al. (1968), using 15 μ m spheres, demonstrated an increase in the fraction of CO to the lungs from 2.5 per cent in the conscious dog, to 17.4 per cent in the pentobarbital-anaesthetised dog. Ahlgren et al. (1978) investigated dogs sedated with a single dose of thiopental and anaesthetised with halothane. Using 50 μ m spheres, no change in a-v shunting was found during short halothane

anaesthesia, but a great increase after two hours of anaesthesia when the influence of thiopental should be of minor importance. In the present study, using halothane/nitrous oxide anaesthesia and 15 μ m spheres, only 1.7 per cent of CO was found in the lungs, indicating a low degree of shunting.

In this investigation, the heart of the conscious rat received 3.8 per cent of CO and there was no reduction during anaesthesia, although myocardial work, as judged from left cardiac work decreased by approximately 30 per cent. This indicates that myocardial oxygenation is well maintained.

10.5 per cent of CO was delivered to the kidneys in the conscious rat and anaesthesia did not change renal blood flow. Miller et al. (1980) and Ross and Daggy (1981), finding similar values in the awake animal, reported a significant increase in the fractional distribution of CO during anaesthesia. However, renal blood flow was maintained also in their studies, as the CO was significantly decreased. This indicates preserved renal autoregulation during halothane anaesthesia.

Reports on the effect of halothane anaesthesia on hepatic arterial blood flow have been conflicting. In this study approximately 7 per cent of CO was distributed to the hepatic artery as compared to 1.5 per cent in the conscious state. There was no concomitant reduction in the fraction delivered to the preportal area. Both Miller et al. (1980) and Ross and Daggy (1981) reported significant increases in the fractional distribution of CO to the hepatic circulation after one hour of anaesthesia, without any simultaneous decrease in preportal flow. This is in contrast to the findings in dogs during halothane anaesthesia, where Ahlgren et al. (1978) found significantly reduced total perfusion. Andreen et al. (1977), using electromagnetic flowmeters, demonstrated decreased blood flow in the hepatic artery in halothane-anaesthetised dogs. This discrepancy between experimental studies in rats and dogs might well be species-dependent.

During prolonged halothane anaesthesia the brain concentration of the anaesthetic increases slowly in spite of the equilibrium in blood (6). As the inspired concentration of halothane was kept constant during the experiment a deeper anaesthesia would be expected. Despite this there were no further changes in mean arterial pressure, cardiac output, heart rate, systemic vascular resistance or left cardiac work between 60 and 90 minutes of halothane/nitrous oxide anaesthesia. Nor was there any change in regional blood flow during this period, and the arterial blood gases revealed no sign of metabolic acidosis.

Considering the minor effects on central haemodynamics and the absence of changes in central and regional haemodynamics between 60 and 90 minutes, this anaesthesia model should be useful in experimental research.

REFERENCES

1. Ahlgren I, Aronsen K F, Björkman I, Wetterlin S. The haemodynamic effects of halothane in the normovolemic dog. *Acta Anaesth Scand* 1978b;22:83-92.
2. Andreen M, Irestedt L, Zetterström B. The different responses of the hepatic arterial bed to hypovolemia and to halothane anaesthesia. *Acta Anaesth Scand* 1977;21:457-469.
3. Archie J, Fixler D, Ulliyot D, Hoffman J, Uteley J, Carlsson E. Measurement of cardiac output with and organ trapping of microspheres. *J Appl Physiol* 1973;35:148-154.
4. Bahlman S H, Eger E J, Smith N T, Stevens W C, Shakespeare T F, Sawyer D C, Halsey M J, Cromwell T H. The cardiovascular effects of nitrous oxide-halothane anaesthesia in man. *Anesthesiology* 1971;35:274-285.
5. Bergman G, Husberg B. A method for multiple intraarterial injections in the allogenic or isogenic transplanted rat kidney by use of a long term catheter in the renal artery. *Scand J Urol Nephrol Suppl* 1980;54:116-119.
6. Duncan W A M, Raventos J. The pharmacokinetics of halothane (fluothane) anaesthesia. *Br J Anaest* 1959;31:302-315.
7. Eger E I, Smith N T, Stoelting R K, Cullen D J, Kadis L B, Witcher C E. Cardiovascular effects of halothane in man. *Anesthesiology* 1970;32:396-407.
8. Engqvist A, Brandt M R, Fernandes A, Kehlet A. The blocking effect of epidural analgesia on the adreno-cortical and hyperglycemic responses to surgery. *Acta Anaesth Scand* 1977;21:330-335.
9. Idvall J, Aronsen K F, Nilsson L, Nosslin B. Evaluation of the microsphere method for determination of cardiac output and flow distribution in the rat. *Eur Surg Res* 1979;11:423-433.

10. Kaihara S, Rutherford R, Schwenker E, Wagner H N Jr. Distribution of cardiac output in experimental hemorrhagic shock in dogs. *J Appl Physiol* 1969;27:218-222.
11. Lees M H, Hill J, Ochsner A J, Thomas C. Regional blood flows of the rhesus monkey during halothane anaesthesia. *Anesth Analg* 1971;50:270-281.
12. Loarie D J, Wilkinson P, Tyberg J, White A. The haemodynamic effects of halothane in anemic dogs. *Anesth Analg* 1979;58:195-200.
13. Miller E D, Kistner J R, Epstein R M. Whole-body distribution of radioactively labelled microspheres in the rat during anaesthesia with halothane, enflurane or ketamine. *Anesthesiology* 1980;52:296-302.
14. Prys-Roberts C (Editor). *The circulation in anaesthesia. Applied physiology and pharmacology.* (Blackwell Scientific Publications, 1980).
15. Raventos J. The action of fluothane, a new volatile anesthetic. *Brit J Pharmacol* 1956;11:394-410.
16. Ross W T Jr, Daggy B P. Hepatic blood flow in phenobarbital-pretreated rats during halothane anaesthesia and hypoxia. *Anesth Analg* 1981;60:306-309.
17. Rudolph A M, Heymann M A. The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circ Res* 1967;21:163-184.
18. Sasaki Y, Wagner H N Jr. Measurements of distribution of cardiac output in unanaesthetized rats. *J Applied Physiol* 1971;30:879-884.
19. Severinghaus J W, Cullen S C. Depression of myocardium and body oxygen consumption with Fluothane in man. *Anesthesiology* 1958;19:165-177.

20. Smith N T, Eger E I, Stoelting R K, Whayne T F, Cullen D, Kadis L B. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. *Anesthesiology* 1970;32:410-421.
21. Smith A L. The mechanism of cerebral vasodilation by halothane. *Anesthesiology* 1973;39:581-587.
22. Svedman P. Cardiac output distribution in animals measured with radioactive dextran microspheres. Thesis, Malmö 1979.

IV

CENTRAL AND PERIPHERAL CIRCULATION DURING AND AFTER
SODIUM NITROPRUSSIDE INDUCED HYPOTENSION IN THE RAT

C. Gustafson

ABSTRACT

Central haemodynamics and regional blood flow were investigated during and after sodium nitroprusside (SNP) infusion in halothane anaesthetised rats. The administration of SNP, $40 \mu\text{g kg}^{-1} \text{min}^{-1}$, reduced mean arterial pressure (MAP) from 97 (mean) mm Hg to 52 (mean) mm Hg. Cardiac output (CO) remained unchanged, while heart rate (HR) and systemic vascular resistance (SVR) decreased. The regional blood flow in the splanchnic organs increased.

When the SNP infusion was stopped MAP rapidly returned to, but not above, the initial level. Fifteen minutes later CO was increased, while SVR and HR remained decreased. Cerebral, myocardial and renal perfusion increased and the changes in the splanchnic area persisted. It is obvious, that although MAP is readily reversed upon withdrawal of SNP, central and regional haemodynamic effects are more protracted.

INTRODUCTION

Hypotensive anaesthesia is often used to diminish surgical bleeding and to provide an easily accessible operation field. Sodium nitroprusside (SNP) induced hypotension is practised in major orthopedic surgery (Lawson et al. 1976, Thompson et al. 1978, Rosberg et al. 1982), ear, nose and throat surgery (Wildsmith et al. 1973, MacRae et al. 1981) as well as in neurosurgery (Stoelting et al. 1977, Lagerkranser et al. 1980, Larsen et al. 1982). However, reports have been published on rebound hypertension following cessation of SNP (Khambatta et al. 1979, Rudehill et al. 1979).

Central haemodynamic effects of SNP have been investigated in the dog (Ross and Cole 1973, Rowe and Hendersson 1974, Wang et al. 1977, Todd et al. 1982). However, only few studies concern whole-body distribution of CO during SNP induced hypotension (Miletich and Ivankovich 1978, Delaney and Miller 1979, Hoffman et al. 1982). To our knowledge, no reports on regional blood flow follow-

ing withdrawal of SNP have been published.

The aim of the present investigation was to determine central haemodynamics and regional blood flow in the rat, during and after SNP induced hypotension.

MATERIAL AND METHODS

Twelve male Wistar rats, weight 248 g (range 205–285 g) were anaesthetised with halothane. Six rats were used as controls (group I), while six rats were investigated during and after SNP induced hypotension (group II).

The investigation was approved by the Regional Committee of Ethics in Animal Experiments.

Animal preparation

Just prior to the experiment, the animals were anaesthetised with halothane/N₂O/O₂. A specially prepared polyethylene catheter, (PE 10), was introduced into the left ventricle of the heart via the right carotid artery, using a metal stylet (Sasaki and Wagner, 1971). The correct position of this catheter was finally verified at necropsy. One PE 90 catheter was introduced into the abdominal aorta and one into the inferior caval vein, via the femoral vessels. The catheters were flushed with heparinised NaCl, 0.9 per cent, and clamped.

Anaesthesia

After catheterisation the rats were tracheotomised, placed supine and connected to a small animals' ventilator (Braun AG, Melsungen, Germany). Anaesthesia was maintained with 1 per cent halothane and nitrous oxide 60 per cent in oxygen (Gustafson et al. 1983).

Hypotension

A freshly prepared solution of sodium nitroprusside, 1 mg/ml in glucose 5.5 per cent, was infused intravenously using an infusion pump (model 355, Sage Instruments, Cambridge, Mass., USA). Infusion rate was adjusted to achieve a mean arterial pressure (MAP)

of 50 mm Hg (6.7 kPa). The average amount of SNP used was $40 \mu\text{g kg}^{-1} \text{ min}^{-1}$.

Mean arterial pressure (MAP mm Hg) was continuously measured by a transducer (EMT 34, Siemens Elema, Sweden) connected to the aortal catheter.

Heart rate (HR, beats min^{-1}) was calculated from the pressure recordings.

Systemic vascular resistance (SVR, dyne $\times \text{sec} \times \text{cm}^{-5}$) was derived from the formula $\text{SVR} = \frac{\text{MAP}}{\text{CO}}$, where CO denotes cardiac output.

Left cardiac work (LCW, kPa $\times \text{l} \times \text{sec}^{-1}$) was calculated from the formula $\text{LCW} = \text{MAP} \times \text{CO}$.

Microspheres type NEN-TRAC (NEN Co, New England, USA) of 15 ± 1 (SD) μm diameter and labelled with ^{46}Sr or ^{103}Ru were used. Depending on the radioactivity 1×10^5 to 2×10^5 spheres were injected each time into the left ventricle during a 3 - 5 second period.

Cardiac output (CO, $\text{l} \times \text{min}^{-1}$) was determined using the reference sample method (Archie et al. 1973, Idvall et al. 1979). Blood was withdrawn from the aortal catheter at a rate of $0.6 \text{ ml} \times \text{min}^{-1}$ for 30 seconds using a withdrawal pump (model 351, Sage Instruments, Cambridge, Mass., USA). Cardiac output was calculated using the formula $\text{CO} = Q_r \times \frac{I_t F}{I_r}$, where Q_r = withdrawal rate, I_t = total injected radioactivity and I_r = radioactivity of the reference sample. F is a conversion factor necessary as I_t and I_r are obtained by two different gamma spectrometers.

Measurements of radioactivity and calculation of regional blood flow

The technique for measuring organ blood flow was the same as that used for rats in earlier investigations from our laboratory (Idvall et al. 1979, Gustafson et al. 1983). Organ blood flow was obtained by multiplying CO by the fractional distribution of CO

to each organ.

Arterial pH, PCO_2 , PO_2 and standard bicarbonate were analysed from 0.5 ml samples of blood (ABL 1, Radiometer, Denmark).

Haematocrit (EVF, %) was determined in duplicate, using 20 μ l blood. The heparinised microtubes were centrifuged at 1000 g for 10 minutes.

Experimental protocol

In group I, MAP and HR were recorded and arterial blood gases analysed after 90 minutes of anaesthesia. At the same time regional blood flow and CO were determined, using radioactive microspheres labelled with ^{46}Sc .

In group II, MAP was reduced to 50 mm Hg (6.7 kPa) after 60 minutes of stable anaesthesia. Fifteen minutes after achieved hypotension, CO and regional blood flow were measured, using microspheres labelled with ^{46}Sc . At the same time MAP, HR and arterial blood gases were determined. Fifteen minutes after termination of SNP CO and regional blood flow were measured again, now using microspheres labelled with ^{103}Ru . MAP and HR were determined at the same time.

In both groups the blood withdrawn for analysis was replaced by a 3-fold volume of saline.

Statistical method

The Mann-Whitney test for unpaired observations was used between the groups. The degrees of significance are marked in the following manner:

* $p \leq 0.05$, ** $p \leq 0.01$

RESULTS

The animals tolerated the experimental procedure well and no arrhythmia was observed. Haematocrit values showed only minor decreases during the study. A mean arterial pressure of 52 mm Hg (6.9 kPa) was achieved within 1 to 2 minutes following the

start of the SNP infusion (Figure 1). Approximately $40 \mu\text{g kg}^{-1}$ was infused during the hypotensive period. The initial infusion rate had to be slightly increased in order to maintain MAP at 50 mm Hg. After cessation of the SNP infusion, MAP almost immediately returned to the initial level (Figure 1).

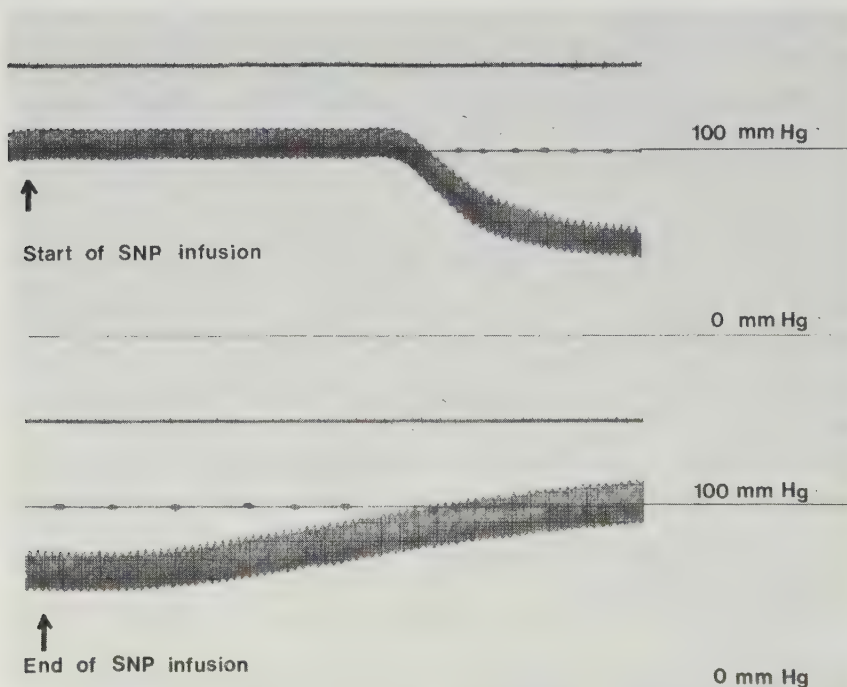


Fig.1. Pressure recording from one rat. Time indication 1 second.

During induced hypotension MAP^{**} , HR^{**} , SVR^{**} , and LCW^* , were reduced as compared to the controls, i.e. group I. CO increased, although not significantly (Table I).

Table II shows the fractional distribution of CO. There was

Table I. Central haemodynamics and arterial blood gases after 90 minutes of halothane/ N_2O/O_2 anaesthesia (group I), 15 minutes after SNP induced hypotension and 15 minutes after reversal of hypotension (group II).

The animals in group II are compared to the controls, i.e. group I, using the Mann-Whitney test for unpaired data.

Degree of significance: ** $p \leq 0.01$.

	Group I		Group II	
	90 minutes of anaesthesia	15 minutes of hypotension	15 minutes after reversal	
MAP, mm Hg	MEAN $\pm$ SE 103 $\pm$ 8	MEAN $\pm$ SE 52** $\pm$ 2	MEAN $\pm$ SE 99 $\pm$ 6	
HR, beats min ⁻¹	437 $\pm$ 9	373** $\pm$ 9	383** $\pm$ 11	
CO/kg, l $\times$ min ⁻¹ $\times 10^{-3}$	291 $\pm$ 21	362 $\pm$ 40	430** $\pm$ 25	
SVR, dyne $\times$ sec $\times$ cm ⁻⁵ $\times 10^3$	117 $\pm$ 4	47** $\pm$ 4	72** $\pm$ 5	
LCW, kPa $\times$ l $\times$ sec ⁻¹ $\times 10^{-3}$	15.6 $\pm$ 0.9	10.6* $\pm$ 1.4	23.5** $\pm$ 2.5	
EVF, %	41 $\pm$ 0.7	40* $\pm$ 0.7	38* $\pm$ 0.6	
pH	7.41 $\pm$ 0.01	7.41 $\pm$ 0.01		
PCO ₂ , kPa	4.5 $\pm$ 0.2	5.2* $\pm$ 0.2		
PO ₂ , kPa	17.8 $\pm$ 1.3	15.4 $\pm$ 0.2		
Stand.bic.	22 $\pm$ 0.9	25 $\pm$ 0.3		

Table II. Fractional distribution of CO after 90 minutes of halothane/N₂O/O₂ anaesthesia (group I), 15 minutes after SNP induced hypotension and 15 minutes after reversal of hypotension (group II). The animals in group II are compared to the controls, i.e. group I, using the Mann-Whitney test for unpaired data. Degree of significance: ** p ≤ 0.01

	Group I		Group II	
	90 minutes of anaesthesia	15 minutes of hypotension	15 minutes after reversal	
	MEAN ± SE	MEAN ± SE	MEAN ± SE	%
Brain	3.5 ± 0.3	4.0 ± 0.5	4.6* ± 0.5	%
Heart	3.3 ± 0.4	4.2 ± 0.6	5.3* ± 0.6	
Lungs ¹	1.7 ± 0.5	2.2 ± 0.6	2.9 ± 0.8	
Kidneys	11.4 ± 0.8	9.8 ± 0.4	12.6 ± 0.6	
Spleen	0.8 ± 0.1	1.6** ± 0.2	1.2 ± 0.2	
Stomach	1.2 ± 0.3	1.3 ± 0.2	1.4 ± 0.1	
Small intestine	9.3 ± 1.0	14.7* ± 1.6	16.1** ± 2.2	
Large intestine	4.3 ± 0.4	4.8 ± 0.6	5.6 ± 0.7	
Liver (Hepatic artery)	7.4 ± 0.7	3.7** ± 0.6	4.1* ± 0.9	
Derived values:				
Preportal area	15.4 ± 1.4	22.3* ± 2.1	24.5** ± 2.8	
Total liver	23.9 ± 1.8	26.1 ± 1.9	28.6 ± 2.3	
Carcass	53 ± 1.6	51 ± 2	44* ± 3	

¹including arteriovenously shunted microspheres from the systemic circulation.

Table III. Individual organ blood flow after 90 minutes of halothane/ $N_2O/0_2$ anaesthesia (group I), 15 minutes after SNP induced hypotension and 15 minutes after reversal of hypotension (group II). The animals in group II are compared to the controls, i.e. group I, using the Mann-Whitney test for unpaired data. Degree of significance: ** $p \leq 0.01$

	Group I		Group II	
	90 minutes of anaesthesia $ml \times g^{-1} \times min^{-1}$	15 minutes of hypotension $ml \times g^{-1} \times min^{-1}$	15 minutes after reversal	
Brain	MEAN $\pm$ SE 1.4 ± 0.2	MEAN $\pm$ SE 2.1 ± 0.4	MEAN $\pm$ SE $2.5^* \pm 0.3$	
Heart	3.8 ± 0.4	6.7 ± 2.1	$8.1^{**} \pm 1.0$	
Lungs ¹	0.9 ± 0.2	1.1 ± 0.3	1.8 ± 0.5	
Kidneys	3.6 ± 0.2	3.5 ± 0.4	$4.9^{**} \pm 0.2$	
Spleen	0.9 ± 0.1	$3.3^{**} \pm 1.1$	$2.4^{**} \pm 0.4$	
Stomach	0.6 ± 0.1	0.8 ± 0.1	1.1 ± 0.1	
Small intestine	1.2 ± 0.1	$2.2^{**} \pm 0.3$	$2.9^{**} \pm 0.5$	
Large intestine	1.4 ± 0.2	1.7 ± 0.2	$2.5^* \pm 0.4$	
Liver (Hepatic artery)	0.4 ± 0.01	$0.3^* \pm 0.04$	0.3 ± 0.04	
Derived values: Flow, $ml \times min^{-1}$				
Preportal area	10.7 ± 1.1	$20.2^{**} \pm 2.7$	$26.6^{**} \pm 3.0$	
Total liver	16.5 ± 1.0	$24.9^{**} \pm 2.9$	$30.9^{**} \pm 2.2$	
Carcass	37.5 ± 3.2	46.6 ± 4.8	48.3 ± 5.2	

¹ including arteriovenously shunted microspheres from the systemic circulation.

an increase in the fractions delivered to spleen^{**}, small intestine^{*}, and preportal area^{*}. Hepatic arterial fraction^{**} decreased.

The corresponding regional blood flow is shown in Table III. Perfusion of spleen^{**} and small intestine^{*} increased. Hepatic arterial flow^{*} was decreased, while preportal^{**} and total liver flow^{*} increased.

Arterial PCO₂^{*} increased, but no other change was found in the blood gases (Table I).

On withdrawal of SNP, MAP rapidly returned to the initial level. Fifteen minutes later HR^{**} and SVR^{**} were still decreased, while CO^{**} and LCW^{**} were increased (Table I).

There was an increase in the fractions of CO distributed to brain^{*}, heart^{*}, small intestine^{**}, and preportal area^{**} as compared to the controls (Table II). Hepatic arterial fraction^{*} remained decreased and the carcass fraction^{*} was reduced.

Perfusion of brain^{*}, heart^{**}, kidneys^{**}, spleen^{**}, and intestine^{**} increased. Preportal^{**} and total liver flow^{**} was increased (Table III).

DISCUSSION

The average amount of SNP used in this study, 40 $\mu\text{g kg}^{-1} \text{ min}^{-1}$, is the same as that given by Hoffman et al. (1982) to rats during halothane anaesthesia. Depending on the influence of the anaesthetic, variable amounts of SNP are needed to achieve the desired hypotension. Miller et al. (1977) used 160 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ to achieve the same degree of hypotension in rats during enflurane anaesthesia.

In the present investigation hypotension was maintained only for 15 minutes. However, a small increase in the infusion rate of SNP was needed to maintain MAP at 50 mm Hg. This tendency to tachyphylaxis might depend on activation of the renin-angiotensin system (Miller et al. 1977) and/or on an increased sympathetic

activity (Rawlinson et al. 1978, Todd et al. 1982).

No changes in central haemodynamics or regional blood flow occur between 60 and 90 minutes of halothane anaesthesia with controlled ventilation (Gustafson et al. 1983). In the present study measurements were performed within this period. Thus, the recorded changes should be attributed to the effects of SNP.

Heart rate decreased significantly during hypotension. In the study of Hoffman et al. (1982) HR in rats did not change during SNP induced hypotension. This is in contrast to the increased HR often seen in young patients (Wildsmith et al. 1973, Rudehill et al. 1979, Khambatta et al. 1979). Miller et al. (1977) suggested that rats have such fast and variable HR that it can not be considered a good estimate of sympathetic activity.

In the rat, induction of halothane anaesthesia is accompanied by an increased hepatic arterial flow, while preportal flow is unchanged (Miller et al. 1980, Gustafson et al. 1983). During hypotension, the reduction found in hepatic arterial flow was less than the increase in preportal flow in the present study. Thus, culculated total hepatic flow was significantly increased, in agreement with the findings of Delaney and Miller (1979).

No metabolic acidosis was found during hypotension, but there was an increased arterial PCO_2 . This might be secondary to an increased physiological dead space during hypotension (Askrog et al. 1964).

When the SNP infusion was stopped, MAP rapidly returned to the initial level. Thus, the reports on rebound hypertension following withdrawal of SNP (Miller et al. 1977, Khambatta et al. 1979, Rudehill et al. 1979) could not be confirmed in this investigation.

Following cessation of the drug CO increased significantly, and blood was diverted from the periphery to increase the perfusion of brain, heart, kidneys, and gut as compared to the control rats (group I). Thus, there are regional differences in the flow distri-

bution after reachieving normotension as compared to the situation before the SNP infusion. The reason for this is not obvious. It might depend on remaining drug, although the half-life of SNP is considered to be only a few minutes in rats (Höbel and Raithel-hüber, 1976). It might also be, that the effect of SNP is prolonged in certain vascular beds.

Myocardial perfusion increased by approximately 60 per cent. At the same time left cardiac work was significantly increased as compared to halothane anaesthetised rats (group I). This agrees with the statement of Allela et al. (1955) and Berne (1964), who found coronary flow to be regulated primarily by cardiac work.

Fifteen minutes after cessation of the SNP infusion, cerebral blood flow was significantly increased, indicating persistent cerebral vasodilation. This is supported by the findings of Auer (1978), demonstrating protracted vasodilation of pial vessels following withdrawal of SNP in a study of cats. Thus, both the elevated MAP and the increased CO may augment cerebral blood flow in the present investigation. These findings are in agreement with other reports (Ivankovich et al. 1976, Turner et al. 1977), suggesting that SNP may compromise cerebral autoregulation.

After withdrawal of SNP, renal perfusion increased significantly. This increase was caused by the elevated CO, since the renal fraction of CO was unchanged. Thus, the normal regulation of renal blood flow did not work. Also the splanchnic circulation was increased, with significantly enhanced perfusion of spleen, intestine, preportal area, and total liver flow. Apparently the effect of SNP is protracted also in the renal vascular bed and the splanchnic area.

Thus, it is obvious that when SNP is withdrawn its haemodynamic effects persist long after the rapid reversal of mean arterial blood pressure.

REFERENCES

- Allela A , Williams F, Bolene-Williams C, Katz L. Interrelation between cardiac oxygen consumption and coronary blood flow. *Am J Physiol* 1955;183:570-582.
- Archie J, Fixler D, Ulliyot D, Hoffman J, Utley J, Carlsson E. Measurements of cardiac output with and organ trapping of microspheres. *J Appl Physiol* 1973;35:148-154.
- Askrog V F, Pender J W, Eckenhoff J E. Changes in physiological dead space during deliberate hypotension. *Anesthesiology* 1964; 25:744-751.
- Auer L. The action of sodium nitroprusside on pial vessels. *Acta Neurochir* 1978;43:297-306.
- Berne R M. Regulation of coronary blood flow. *Physiol Rev* 1964; 44:1-29.
- Delaney T J, Miller Jr E D. Blood flow alterations induced by saralasin or SNP. *Anesthesiology* 1979;51:73.
- Gustafson C, Aronsen K F, Idvall J, Rosberg B. Central haemodynamics and regional blood flow during halothane-nitrous oxide anaesthesia and controlled ventilation. *Res Exp Med* 1983: In press.
- Hoffman W E, Satinover I, Miletich D J, Albrecht R F, Gans B J. Cardiovascular changes during SNP or ATP infusion in the rat. *Anesth Analg* 1982;61:99-103.
- Höbel M, Raitelhuber A. Untersuchungen über den Stoffwechsel und die Organverteilung von ¹⁴C-markiertem Natrium-nitroprussid an Ratten. *Arzneim -Forsch (Drug Res)* 1976;26:2015-2019.
- Idvall J, Aronsen K F, Nilsson L, Nosslin B. Evaluation of the microsphere method for determination of cardiac output and flow distribution in the rat. *Eur Surg Res* 1979;11:423-433.

- Ivankovich A D, Miletich D J, Albrecht R F, Zahed B. Sodium nitroprusside and cerebral blood flow in the anesthetised and unanesthetised goat. *Anesthesiology* 1976;44:21-26.
- Khambatta H J, Stone J G, Khan E. Hypertension during anesthesia on discontinuation of SNP induced hypotension. *Anesthesiology* 1979;51:127-130.
- Lagerkranser M, Gordon E, Rudehill A. Cardiovascular effects of SNP in cerebral aneurysm surgery. *Acta Anaesth Scand* 1980;24:426-432.
- Larsen R, Teichmann J, Hifiker O, Busse C, Sonntag H. Nitroprusside hypotension: Cerebral blood flow and cerebral oxygen consumption in neurosurgical patients. *Acta Anaesth Scand* 1982;26:327-330.
- Lawson N W, Thompson D S, Nelson C L, Flacke J W, North E R. Sodium nitroprusside induced hypotension for supine total hip replacement. *Anesth Analg* 1976;55:654-662.
- MacRae W R, Wildsmith J A W, Dale B A B. Induced hypotension with a mixture of SNP and TMP. *Anaesthesia* 1981;36:312-315.
- Miletich D J, Ivankovich A D. Sodium nitroprusside and cardiovascular hemodynamics. *Int Anesth Clin* 1978;16:31-49.
- Miller E D, Ackerly J A, Vaughan Jr E D, Peach M J, Epstein R M. The renin angiotensin system during controlled hypotension with sodium nitroprusside. *Anesthesiology* 1977;47:257-262.
- Miller E D, Kistner J R, Epstein R M. Whole-body distribution of radioactively labelled microspheres in the rat during anesthesia with halothane, enflurane or ketamine. *Anesthesiology* 1980;52:296-302.
- Rawlinson W A L, Loach A B, Benedict C R. Changes in plasma concentration of adrenaline and noradrenaline in anaesthetised patients during sodium nitroprusside induced hypotension. *Br J Anaesth* 1978;50:937-943.

- Rosberg B, Fredin H, Gustafson C. Anesthetic techniques and surgical blood loss in total hip arthroplasty. *Acta Anaesth Scand* 1982;26:189-193.
- Ross G, Cole P V. Some cardiovascular actions of sodium nitroprusside in the dog. *Br J Anaesth* 1973;45:120.
- Rowe G G, Henderson R H. Systemic and coronary hemodynamic effects of sodium nitroprusside. *Amer Heart J* 1974;87:83-87.
- Rudehill A, Gordon E, Lagerkranser M. Sodium nitroprusside as a hypotensive agent in intracranial aneurysm surgery. *Acta Anaesth Scand* 1979;23:404-410.
- Sasaki Y, Wagner H N Jr. Measurements of distribution of cardiac output in unanaesthetised rats. *J Appl Physiol* 1971;30:879-884.
- Stoelting R K, Viegas O, Campbell R L. Sodium nitroprusside produced hypotension during anesthesia and operation in the head up position. *Anesth Analg* 1977;56:391-394.
- Thompson G E, Miller R D, Stevens W C, Murray W R. Hypotensive anesthesia for total hip arthroplasty: A study of blood loss and organ function (brain, heart, liver and kidney). *Anesthesiology* 1978;48:91-96.
- Todd M M, Morris P J, Moss J, Philbin D M. Hemodynamic consequences of abrupt withdrawal of nitroprusside or nitroglycerine following induced hypotension. *Anesth Analg* 1982;61:261-266.
- Turner J M, Powell D, Gibson R M, McDowall D G. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br J Anaesth* 1977;49:419-425.
- Wang H H, Liu L M P, Katz R L. A comparison of the cardiovascular effects of SNP and TMP. *Anesthesiology* 1977;46:40-48.

Wildsmith J A W, Marshall R L, Jenkinson J L, MacRae W R,
Scott D B. Haemodynamic effects of sodium nitroprusside
during nitrous oxide/halothane anaesthesia. Br J Anaesth
1973;45:71-74.

V

CIRCULATORY EFFECTS OF HAEMORRHAGE DURING

SODIUM NITROPRUSSIDE INDUCED HYPOTENSION

A study in the rat.

C. Gustafson, K.F. Aronsen and B. Rosberg

ABSTRACT

The haemodynamic changes induced by acute moderate blood loss were investigated in rats during normotensive halothane anaesthesia, and during sodium nitroprusside (SNP) induced hypotensive anaesthesia, respectively.

Following haemorrhage in the normotensive group, mean arterial blood pressure, heart rate and left cardiac work decreased. Cardiac output was reduced non-significantly. Blood flow was redistributed to favour cerebral, coronary, renal and hepatic circulation, mainly at the expense of blood flow to the carcass.

Following haemorrhage in the hypotensive group cardiac output increased significantly. Mean arterial pressure, heart rate and left cardiac work were unchanged. Absolute values for cerebral, coronary, renal and hepatic blood flow were maintained or even increased while blood flow to the carcass was unchanged.

INTRODUCTION

Hypotensive anaesthesia with sodium nitroprusside (SNP) is practised chiefly in order to reduce surgical blood loss (1,2,3). Most studies of the haemodynamic effects of SNP have been performed in normovolaemic man (4,5), or animal (6,7,8,9,10).

Acute blood loss stimulates the sympatho-adrenal system, leading to cardiostimulation and peripheral vasoconstriction (11). Blood flow is redistributed from the periphery to favour organs of importance for immediate survival, i.e. brain, heart and liver (12, 13,14,15). Studies on animals with compromised vasoconstriction due to surgical sympathectomy (16,17), or to adrenoceptor blocking drugs (18,19) give diverging information on their tolerance to blood loss.

SNP, which causes vasodilation by its effect on vascular smooth muscle (20), might influence the haemodynamic response to blood loss.

In clinical work, patients might develop hypovolaemia during SNP induced hypotension. To our knowledge no data have been published on the circulatory consequences of acute hypovolaemia during SNP induced hypotensive anaesthesia.

The aim of the present investigation was to study the haemodynamic response to withdrawal of a fixed volume of blood in rats during SNP induced hypotensive anaesthesia.

MATERIAL AND METHODS

Fourteen male Wistar rats, mean weight 241 g (range 165–310 g) were subjected to moderate haemorrhage under halothane anaesthesia. Seven of the rats were investigated during normotensive halothane anaesthesia (group I, control) and seven were studied during SNP induced hypotension (group II).

The investigation was approved by the Regional Committee of Ethics in Animal Experiments.

Animal preparation

Just prior to the experiment, the animals were anaesthetised with halothane/N₂O/O₂. A specially prepared polyethylene catheter (PE 10), was introduced into the left ventricle of the heart (21). The correct position of this catheter was verified at necropsy. One PE 90 catheter was introduced into the abdominal aorta and one into the inferior caval vein via the femoral vessels. The catheters were flushed with heparinised NaCl, 0.9 per cent, and clamped.

Anaesthesia

After catheterisation the rats were tracheotomised, placed supine and connected to a small animals' ventilator (Braun AG, Melsungen, Germany). The gas mixture delivered, was 1 per cent halothane, as checked spectrophotometrically (EMMA, Engström Medicals, Sweden), and 60 per cent nitrous oxide in oxygen. This is the lowest halothane concentration which, in combination with nitrous oxide,

gives loss of the corneal and righting reflexes (22).

Ventilation rate was fixed at 80 min^{-1} , and tidal volume adjusted to keep an arterial PCO_2 of approximately 4.5 kPa. The body temperature of the animals was kept around 37°C , using a warming lamp.

Hypotension

A freshly prepared solution of sodium nitroprusside 1 mg/ml, in glucose 5.5 per cent, was infused i.v. using an infusion pump (model 355, Sage Instruments, Cambridge, Mass., USA). Infusion rate was adjusted to achieve a mean arterial pressure (MAP) of 50 mm Hg (6.7 kPa). The average amount of SNP used was $40 \mu\text{g/kg}$ body weight.

Mean arterial pressure (MAP, mm Hg) was measured by a transducer (EMT 34, Siemens Elema, Sweden) connected to the aortal catheter.

Heart rate (HR) was calculated from the pressure recordings.

pH, PCO_2 , PO_2 and standard bicarbonate were analysed from 0.5 ml samples of arterial blood (ABL 1, Radiometer, Denmark).

Haematocrit (EVF, %) was determined in duplicate, using $20 \mu\text{l}$ blood. The heparinised microtubes were centrifuged at 1000 g for 10 minutes.

Systemic vascular resistance (SVR, $\text{dyne} \times \text{sec} \times \text{cm}^{-5}$) was derived from the formula $\text{SVR} = \frac{\text{MAP}}{\text{CO}}$ where CO denotes cardiac output.

Left cardiac work (LCW, $\text{kPa} \times \text{l} \times \text{sec}^{-1}$) was calculated from the formula $\text{LCW} = \text{MAP} \times \text{CO}$.

Microspheres type NEN-TRAC (NEN Co, New England, USA) of 15 ± 1 (SD) μm diameter and labelled with ^{46}Sc or ^{103}Ru were used. Depending on the activity, 1×10^5 to 2×10^5 spheres were injected into the left ventricle during a 3-5 second period.

Cardiac output (CO, $\text{l} \times \text{min}^{-1}$) was determined using the reference sample method (23,24). Blood was withdrawn from the aortal catheter.

ter at a rate of $0.6 \text{ ml} \times \text{min}^{-1}$ for 30 seconds using a withdrawal pump (model 351, Sage Instruments Cambridge, Mass., USA). Cardiac output was calculated using the formula

$\text{CO} = Q_r \times \frac{I_t F}{I_r}$, where Q_r = withdrawal rate, I_t = total injected radioactivity and I_r = radioactivity of the reference sample. F is a conversion factor necessary as I_t and I_r are obtained by two different gamma spectrometers.

Regional blood flow. The total amount of injected radioactivity was determined by measuring the whole rat in a lead-shielded detector. The detector was connected to a gamma spectrometer (Canberra model 818) with window settings at 450-550 keV (^{103}Ru) and 700-1000 keV (^{46}Sc). Animal standards were used to correct for overlapping of the isotopes. The organs were removed, weighed and put into small plastic tubes. Large organs were divided. The inner lining of the left ventricle and the valvular cusps were excised to avoid an incorrect value for myocardial blood flow (4).

Concentrated sulphuric acid was added to homogenise the tissues in order to minimise geometrical error. The activity of the specimens was determined in an automatic well counter (2 x 2 inch well crystal, Nuclear, Chicago). Standard solutions of the isotopes were used to correct for isotope overlapping. Carcass activity was determined in the scintillation detector after organ removal.

Experimental protocol

In group I, measurements of MAP, HR, EVF and blood gases were carried out after 60 minutes of stable anaesthesia. At the same time regional blood flow and CO were determined, using microspheres labelled with ^{46}Sc . Thereafter blood, 10 ml/kg body weight, was withdrawn via the arterial catheter for a period of 2 minutes. Twenty minutes later the measurements were repeated, now using microspheres labelled with ^{103}Ru .

In group II, SNP hypotension (MAP = 50 mm Hg) was induced after 45 minutes of stable halothane anaesthesia. Fifteen minutes after

induced hypotension, the measurements described above were performed, using microspheres labelled with ^{46}Sc . Acute blood loss was accomplished in the same way as in group I, and 20 minutes later, the last set of measurements were carried out using microspheres labelled with ^{103}Ru .

In both groups the blood withdrawn for analysis was replaced by a 3-fold volume of saline.

Statistical method

The Wilcoxon test for paired observations was used. The degree of significance is marked as follows:

* $p \leq 0.05$.

RESULTS

After acute blood loss in the control group, MAP, HR and LCW decreased significantly (Table I). The reduction in cardiac output was not significant. Arterial pH and standard bicarbonate were significantly reduced. The haematocrit value decreased significantly by 18 per cent.

Results of measurements of haemodynamics in group II are shown in Table I. Cardiac output was significantly increased, while there was no significant reduction in MAP. Heart rate and LCW were unaffected, whereas SVR decreased significantly.

Standard bicarbonate was significantly decreased 20 minutes after haemorrhage. No other change of the arterial blood gases was found. The haematocrit value decreased significantly by 16 per cent.

In the control group the fraction of cardiac output to the heart, small intestine, hepatic artery, preportal area and total liver increased significantly (Table II). The fractions to the lungs, spleen and carcass were significantly reduced, while the kidney fraction was unchanged. The absolute values of blood flow to the

lungs and spleen decreased significantly, while hepatic arterial flow and total liver perfusion increased significantly. Kidney perfusion was unchanged.

The fractional distribution of cardiac output after blood loss in group II is shown in Table II. The fractions to the lungs, kidneys and spleen were significantly reduced.

The corresponding organ blood flow is shown in Table III. Blood flow to the lungs was significantly reduced. Perfusion of brain, heart, large intestine, hepatic artery, preportal area and total liver increased significantly. Renal perfusion was unchanged.

DISCUSSION

In experimental studies on haemorrhage, two principally different methods are commonly used: either blood volume is reduced to obtain a fixed systolic pressure, or a fixed volume of blood is shed. The constant pressure model would be disadvantageous for the present investigation, as mean arterial pressure is affected in the SNP group. Consequently the blood loss would be unequal for the two groups. Therefore we chose to bleed the rats 10 ml/kg body weight, according to a model previously used in our laboratory (15). The blood volume of the normovolaemic Wistar rat has been determined to 70 ml/kg (15). The blood shed in the present investigation thus corresponds to approximately 15 per cent of the blood volume.

The bleeding procedure was well tolerated and the injections of microspheres did not cause any arrhythmias or reductions in the systemic arterial pressure.

In a previous investigation (22), it was shown that no central or regional haemodynamic changes occur between 60 and 90 minutes of halothane anaesthesia with controlled ventilation. In the present study the measurements were performed within this period. Thus, the registered changes should mainly be attributed to the

Table I. Central haemodynamics and arterial blood gases during normovolaemia and the mean differences after haemorrhage in group I (halothane anaesthesia) and group II (SNP hypotension).

The Wilcoxon test for paired observations was used within the groups. Degree of significance: * $p \leq 0.05$.

	Group I		Group II	
	Normovolaemia	Hypovolaemia	Normovolaemia	Hypovolaemia
	M $\pm$ SEM	M-diff $\pm$ SE-diff	M $\pm$ SEM	M-diff $\pm$ SE-diff
MAP, mm Hg	119 $\pm$ 5	-36* $\pm$ 5	53 $\pm$ 5	-9 $\pm$ 2
HR, beats $\times$ min ⁻¹	441 $\pm$ 8	-47* $\pm$ 12	395 $\pm$ 17	-4 $\pm$ 3
CO/kg, l $\times$ min ⁻¹ $\times 10^{-3}$	223 $\pm$ 17	-34 $\pm$ 10	253 $\pm$ 18	+54* $\pm$ 14
SVR, dyne $\times$ sec $\times$ cm ⁻⁵ $\times 10^3$	183 $\pm$ 22	-28.3 $\pm$ 10.8	76 $\pm$ 6	-24.0* $\pm$ 6.0
LCW, kPa $\times$ l $\times$ sec ⁻¹ $\times 10^{-3}$	14.3 $\pm$ 1.2	-5.6* $\pm$ 0.6	6.8 $\pm$ 2.0	-0.5 $\pm$ 0.3
EVF, %	39 $\pm$ 0.3	-7* $\pm$ 0.5	38 $\pm$ 0.6	-6* $\pm$ 1.0
Arterial blood gases				
pH	7.41 $\pm$ 0.01	0.05* $\pm$ 0.01	7.39 $\pm$ 0.02	0.04 $\pm$ 0.01
PCO ₂ , kPa	4.9 $\pm$ 0.3	+0.5 $\pm$ 0.6	4.9 $\pm$ 0.3	+0.3 $\pm$ 0.1
PO ₂ , kPa	16.6 $\pm$ 0.4	+0.3 $\pm$ 0.6	16.2 $\pm$ 0.7	-0.4 $\pm$ 0.5
Stand. bic., mmol/l	23.7 $\pm$ 0.3	-2.1* $\pm$ 0.3	23.0 $\pm$ 0.6	3.0* $\pm$ 0.4

Table II. Fractional distribution of CO during normovolaemia ($M \pm SEM$), and mean differences after haemorrhage ($M\text{-diff} \pm SE\text{-diff}$) in group I (halothane anaesthesia) and group II (SNP hypotension). The Wilcoxon test for paired observations was used within the groups. Degree of significance: * $p \leq 0.05$.

	Group I			Group II		
	Normovolaemia		Hypovolaemia	Normovolaemia		Hypovolaemia
	$M \pm SEM$	%	$M\text{-diff} \pm SE\text{-diff}$	$M \pm SEM$	%	$M\text{-diff} \pm SEM\text{-diff}$
Brain	4.4 ± 0.5		$+0.9 \pm 0.3$	6.1 ± 0.8		$+0.01 \pm 0.3$
Heart	3.3 ± 0.3		$+1.1^* \pm 0.2$	4.3 ± 0.3		$+0.9 \pm 0.3$
Lungs ¹	2.1 ± 0.4		$-1.3^* \pm 0.3$	1.4 ± 0.3		$-0.7^* \pm 0.2$
Kidneys	11.7 ± 0.7		$+0.9 \pm 0.4$	8.9 ± 0.9		$-1.3^* \pm 0.1$
Spleen	1.0 ± 0.1		$-0.4^* \pm 0.1$	1.6 ± 0.2		$-0.3^* \pm 0.1$
Stomach	1.1 ± 0.1		$+0.1 \pm 0.1$	1.4 ± 0.2		$+0.1 \pm 0.1$
Small intest.	7.8 ± 0.3		$+2.6^* \pm 0.5$	13.9 ± 1.0		-0.4 ± 0.9
Large intest.	3.7 ± 0.3		$+0.3 \pm 0.2$	3.5 ± 0.4		$+0.4 \pm 0.1$
Liver (Hepatic artery)	9.0 ± 0.8		$+5.1^* \pm 0.6$	4.8 ± 0.6		-0.01 ± 0.3
Derived values:						
Preportal area	13.6 ± 0.5		$+2.6^* \pm 0.7$	20.4 ± 1.0		-0.2 ± 0.8
Total liver	22.6 ± 1.0		$+7.7^* \pm 0.6$	25.3 ± 1.0		$+0.2 \pm 0.4$
Carcass	52 ± 2		$-9^* \pm 2$	51 ± 1		$+1 \pm 1$

¹ Including arteriovenously shunted microspheres from the systemic circulation.

Table III. Individual organ blood flow during normovolaemia ($M \pm SEM$), and mean differences after haemorrhage ($M\text{-diff} \pm SE\text{-diff}$) in group I (Halothane anaesthesia) and group II (SNP hypotension). The Wilcoxon test for paired observations was used within the groups. Degree of significance: * $p \leq 0.05$

	Group I		Group II	
	Normovolaemia	Hypovolaemia	Normovolaemia	Hypovolaemia
	$M \pm SEM$	$M\text{-diff} \pm SEM\text{-diff}$	$M \pm SEM$	$M\text{-diff} \pm SEM\text{-diff}$
	$ml \times g^{-1} \times min^{-1}$		$ml \times g^{-1} \times min^{-1}$	
Brain	1.4 ± 0.2	-0.1 ± 0.1	1.8 ± 0.2	$+0.4^* \pm 0.2$
Heart	2.7 ± 0.3	$+0.3 \pm 0.2$	3.4 ± 0.3	$+1.5^* \pm 0.4$
Lungs ¹	0.9 ± 0.2	$-0.6^* \pm 0.1$	0.6 ± 0.1	$-0.3^* \pm 0.1$
Kidneys	3.0 ± 0.4	-0.5 ± 0.2	2.7 ± 0.4	$+0.1 \pm 0.1$
Spleen	0.9 ± 0.1	$-0.4^* \pm 0.1$	2.0 ± 0.4	-0.1 ± 0.1
Stomach	0.4 ± 0.1	-0.03 ± 0.04	0.7 ± 0.1	$+0.2 \pm 0.1$
Small intest.	0.9 ± 0.6	-0.1 ± 0.03	1.5 ± 0.2	$+0.2 \pm 0.1$
Large intest.	1.4 ± 0.3	-0.1 ± 0.04	1.0 ± 0.2	$+0.3^* \pm 0.1$
Liver (Hepatic artery)	0.4 ± 0.03	$+0.1^* \pm 0.04$	0.2 ± 0.02	$+0.1^* \pm 0.04$
Derived values: Flow $ml \times min^{-1}$				
Preportal	7.6 ± 0.8	$+0.03 \pm 0.3$	11.9 ± 1.6	$+2.3^* \pm 0.6$
Total liver	12.4 ± 1.0	$+2.0^* \pm 0.6$	14.8 ± 2.0	$+2.6^* \pm 0.8$

¹ including arteriovenously shunted microspheres from the systemic circulation

effects of hypovolaemia and SNP.

The main difference in regional blood flow distribution between the two groups during normovolaemia is found in the splanchnic area. During SNP induced hypotension the perfusion of spleen, small intestine and portal area is enhanced, while hepatic arterial flow is reduced. This is in agreement with earlier findings (22,25).

Twenty minutes after haemorrhage, HR, MAP and LCW were significantly reduced, CO slightly decreased and SVR unaffected in the control group. These findings are in contrast to those in the SNP group where HR and LCW were unaffected, and no further significant reduction of MAP was found. CO increased significantly, while SVR was significantly decreased.

Reports on HR response to hypovolaemia are conflicting. Castenfors and Sjöstrand (26) observed that following haemorrhage in anaesthetised rats, most animals show bradycardia, mediated by vagal stimulation. This is in agreement with our findings in the control group. Idvall et al. (15) however, demonstrated that conscious rats display tachycardia when subjected to moderate haemorrhage. The unaffected HR in the SNP treated group might be explained by increased sympathetic activity (10,27).

In the control group the reduced HR might have contributed to the great reduction in MAP. In the SNP group MAP was not further significantly reduced during hypovolaemia.

The reasons why cardiac output increased after blood loss in the SNP group cannot be explained by the results of our study. SNP may induce hyperkinetic circulatory changes (6,28). It reduces circulatory afterload (16,29) but has no direct effects on myocardial contractility (30,31). Haemorrhage (11) as well as SNP induced hypotension (10,27) cause an increased sympathetic activity. It seems unlikely, however, that increased sympathetic activity of an extent that does not affect the heart rate would be sufficient to increase cardiac output during hypovolaemia. In addi-

tion, Idvall et al. (15) demonstrated a significant fall in cardiac output after the same amount of blood loss in rats during Ketamine anaesthesia - an agent which has sympathomimetic properties (32).

Alternatively, the full effects of SNP on cardiac output might not have been fully established after 15 minutes. However, in dogs Rowe and Henderson (6) found a maximal increase of cardiac output within the first ten minutes of SNP infusion.

SNP is metabolised in the erythrocytes and plasma (33). During hypovolaemia SNP infusion might lead to higher plasma values than during normovolaemia and consequently cause more pronounced circulatory effects.

Following acute haemorrhage in the control group, blood was redistributed to favour perfusion of immediately vital organs, i.e. brain, heart, kidneys and liver, at the expense of a decreased carcass fraction.

In the SNP group however, perfusion of vital organs was maintained or enhanced as CO increased.

The change of the fractional distribution of CO to the lungs was similar in the two groups. The fraction measured in the lungs with the microsphere method is the sum of the bronchial arterial flow and the systemic arterio-venous shunting. An increased systemic shunting occurs during anaesthesia (34,35). In this investigation values obtained during normovolaemia indicate a low degree of shunting. The reduction following haemorrhage might primarily depend on a reduction in systemic arterio-venous shunting (14).

In the control group, cerebral blood flow was unaffected by blood loss. Thus, halothane in the concentration used in this study does not affect the autoregulation of cerebral circulation. In the SNP group perfusion of the brain increased during hypovolaemia. This might be explained by the effects of SNP on the autoregulation of the cerebral circulation (36,37,38).

Perfusion of the myocardial muscle did not change following haemorrhage in the control group, despite a reduced cardiac work. In the SNP animals, coronary flow increased significantly, while cardiac work was unchanged. Thus, during hypovolaemia, myocardial flow was increased in relation to cardiac work in both groups. This is in contrast to findings during normovolaemia, where changes in cardiac blood flow and work are proportional (39,40). The relatively high blood flow following haemorrhage might represent a compensation to decreased arterial oxygen content (41), and regional ischaemia secondary to redistribution of intramyocardial blood flow (14,42).

SNP might have an additional effect on coronary blood flow, as it has been shown to dilate coronary vessels (6,7).

Renal perfusion was maintained in both groups during hypovolaemia, indicating that the autoregulation was unaffected by the dosage of SNP used. The increased circulation in the small intestine, induced by SNP (25), was maintained, while perfusion of the large bowel increased following haemorrhage. In the control group, perfusion was unaffected.

In the control group, hepatic arterial flow, and total liver perfusion increased significantly following haemorrhage. In the SNP group however, both hepatic arterial flow and preportal flow increased significantly. Thus, in both groups, liver perfusion was well provided for during hypovolaemia.

A slight metabolic acidosis was noted in both groups following haemorrhage. In the control group, this is most likely due to reduced peripheral tissue perfusion during hypovolaemia. In the SNP group CO was increased, and the acidosis might depend on impaired metabolism of SNP during hypovolemia. As suggested by Vesey et al. (43), HCN, a metabolite of SNP, causes metabolic acidosis.

One must be cautious in applying the results of this experi-

mental study to man. However, the effect of moderate haemorrhage during SNP induced hypotension is a preserved perfusion of vital organs, not at the expense of redistribution of carcass perfusion, but due to an increased cardiac output.

REFERENCES

1. Lawson N W, Thompson D S, Nelson C L, Flacke J W, North E R. Sodium nitroprusside induced hypotension for supine total hip arthroplasty. *Anesth Analg* 1976;55:654-662.
2. Barbier-Böhm G, Desmonts J M, Conderc E, Moulin O, Prokocimer P, Olivier H. Comparative effects of induced hypotension and normovolaemic haemodilution on blood loss in total hip arthroplasty. *Br J Anaesth* 1980;52:1039-1043.
3. Rosberg B, Fredin H, Gustafson C. Anaesthetic techniques and surgical blood loss in total hip arthroplasty. *Acta Anaesth Scand* 1982;26:189-193.
4. Rudehill A, Gordon E, Lagerkranser M. Sodium nitroprusside as a hypotensive agent in intracranial aneurysm surgery. *Acta Anaesth Scand* 1979;23:404-410.
5. Khambatta H J, Stone J G, Khan E. Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. *Anesthesiology* 1979;51:127-130.
6. Rowe G G, Hendersson R H. Systemic and coronary hemodynamic effects of sodium nitroprusside. *Amer Heart J* 1974;87:83-87.
7. Wang H H, Liu L M P, Katz R L. A comparison of the cardiovascular effects of sodium nitroprusside and trimethaphan. *Anesthesiology* 1977;46:40-48.
8. Miller Jr E D, Ackerly J A, Vaughan Jr E D, Peach M J, Epstein R M. The renin-angiotensin system during controlled hypotension with sodium nitroprusside. *Anesthesiology* 1977;47:257-262.
9. Hoffman W E, Satinover I, Miletich D J, Albrecht R F, Gans B J. Cardiovascular changes during SNP or ATP infusion in the rat. *Anesth Analg* 1982;61:99-103.

10. Todd M M, Morris P J, Moss J, Philbin D M. Hemodynamic consequences of abrupt withdrawal of nitroprusside or nitroglycerin following induced hypotension. *Anesth Analg* 1982;61:261-266.
11. Chien S. Role of the sympathetic nervous system in haemorrhage. *Physiol Rev* 1967;47:214-288.
12. Ericsson B F. Early effects of haemorrhage on the distribution of cardiac output in the anesthetized dog. *Acta Chir Scand* 1972;138:13-19.
13. Ahlgren I, Aronsen K F, Björkman I, Wetterlin S. The effect of halothane on the distribution of cardiac output and organ blood flow in the hypovolemic dog. *Acta Anaesth Scand* 1978;22:99-107.
14. Rosberg B, Wulff K. Regional blood flow in normovolaemic and hypovolaemic haemodilution. An experimental study. *Br J Anaesth* 1979;51:423-430.
15. Idvall J. Influence of ketamine anesthesia on cardiac output and tissue perfusion in rats subjected to hemorrhage. *Anesthesiology* 1981;55:297-304.
16. Schlossberg T, Sawyer M E M. Studies on the homeostasis in normal, sympathectomized and ergotaminized animals. The effect of hemorrhage. *Am J Physiol* 1933;104:195-203.
17. Brooks C Mc. The reaction of chronic spinal animals to hemorrhage. *Am J Physiol* 1935;114:30-39.
18. Jacob S, Friedman E W, Levenson S, Glotzer P, Frank H A, Fine J. Antiadrenergic and antihistaminic treatment in hemorrhagic shock in dog and man. *Am J Physiol* 1956;186:79-84.
19. Baez S, Srikanti S G, Burack B. Dibenzylamine protection against shock and preservation of hepatic ferritin system. *Am J Physiol* 1958;192:175-180.

20. Johnson C C. The action and toxicity of sodium nitroprusside. *Arch Int Pharmacol Ther* 1929;35:480-496.
21. Sasaki Y, Wagner H N. Measurements of the distribution of cardiac output in unanesthetized rats. *J Appl Physiol* 1971;30: 879-884.
22. Gustafson C, Aronsen K F, Rosberg B. Central haemodynamics and regional blood flow during halothane-nitrous oxide anaesthesia and controlled ventilation. *Res Exp Med*. In press. 1983.
23. Archie Jr J P, Fixler D E, Ulliyot D J, Hoffman J I E, Uttley J R, Carlson E L. Measurements of cardiac output with and organ trapping of radioactive microspheres. *J Appl Physiol* 1973;35:148-154.
24. Idvall J, Aronsen K F, Nilsson L, Nosslin B. Evaluation of the microsphere method for determination of cardiac output and flow distribution in the rat. *Eur Surg Res* 1979;11:423-433.
25. Delaney T J, Miller Jr E D. Blood flow alteration induced by saralasin or SNP. *Anesthesiology* 1979;51:73.
26. Castenfors J, Sjöstrand T. Circulatory control via vagal afferents. Adjustment of heart rate to variations of blood volume in the rat. *Acta physiol scand* 1972;84:347-354.
27. Rawlinson W A L, Loach A B, Benedict C R. Changes in plasma concentration of adrenaline and noradrenaline in anaesthetized patients during sodium nitroprusside-induced hypotension. *Br J Anaesth* 1978;50:937-943.
28. Wildsmith J A W, Marshall R L, Jenkinson J L, McRae W R, Scott D B. Haemodynamic effects of sodium nitroprusside during nitrous oxide/halothane anaesthesia. *Br J Anaesth* 1973;45:71-74.

29. Gerson J I, Allen F B, Seltzer J L, Parker Jr F B, Markowitz A H. Arterial and venous dilation by nitroprusside and nitroglycerin - Is there a difference? *Anest Analg* 1982;61: 256-260.
30. Adams A P, Clarke T N S, Edmonds-Seal J, Foex P, Prys-Roberts C, Roberts J. Effects of sodium nitroprusside on myocardial contractility and haemodynamics. *Br J Anaesth* 1973;45:120.
31. Brodie B R, Cuck L, Klausner S, Grossman W, Parmley W. Effect of sodium nitroprusside and nitroglycerin on tension prolongation of cat papillary muscle during recovery from hypoxia. *Circ Res* 1976;39:596-601.
32. Traber D L, Wilson R D. Involvement of the sympathetic nervous system in the pressor response to ketamine. *Anesth Analg* 1969;48:248-252.
33. Vesey C J, Simpson P J, Adams L, Cole P V. Metabolism of sodium nitroprusside and cyanide in the dog. *Br J Anaesth* 1979;51:89-97.
34. Kaihara, S, Van Herden P O, Migita T, Wagner Jr H N. Measurements of distribution of cardiac output. *J Appl Physiol* 1968;25:696-700.
35. Ohlsson E G. Regional blood flow studies with labelled microspheres of different sizes in dogs with and without occlusion of the common bile duct. *Eur Surg Res* 1971;3:348-362.
36. Ivankovich A D, Miletich D J, Albrecht R F, Zahed B. Sodium nitroprusside and cerebral blood flow in the anesthetized and unanaesthetized goat. *Anesthesiology* 1976;44:21-26.
37. Miletich D J, Gil K S L, Albrecht R F, Zahed B. Intracerebral blood flow distribution during hypotensive anesthesia in the goat. *Anesthesiology* 1980;53:210-214.

38. Turner J M, Powell D, Gibson R M, Mc Dowall D G. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimethaphan. Br J Anaesth 1977;49:419-425.
39. Allella A, Williams F, Bolene-Williams C, Katz L. Inter-relation between cardiac oxygen consumption and coronary blood flow. Am. J Physiol 1955;183:570-582.
40. Berne R M. Regulation of coronary blood flow. Physiol Rev 1964;44:1-29.
41. Race D, Dedichsen H, Schenk Jr W. Regional blood flow during dextran-induced normovolemic hemodilution in the dog. J Thorac Cardiovasc Surg 1967;53:578-586.
42. Winbury M M. Redistribution of left ventricular blood flow produced by nitroglycerine. Circ Res 1971;28 (suppl 1) 140-147.
43. Vesey C J, Cole P V. Nitroprusside and cyanide. Br J Anaesth 1975;47:1115.

